A RETROSPECTIVE STUDY OF THE THORACIC AND ABDOMINAL RADIOGRAPHIC ABNORMALITIES IN CANINE MULTICENTRIC LYMPHOMA

by

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DEDICATION

To Peter, Jim and Pat.

ACKNOWLEDGEMENTS

During the preparation of this dissertation, many of my colleagues at Glasgow University Veterinary School have been of assistance. I would like to specifically acknowledge the contributions of a number of individuals.

The radiographic interpretations presented in this dissertation were carried out in the first instance by three radiologists, including myself. The other interpreters were Dr Martin Sullivan, Lecturer in Soft Tissue Surgery and Radiology, and Ms Helen Lawson, House Surgeon. Without their contributions, this study would have been impossible. In addition, Dr Martin Sullivan advised on many aspects of project design.

The majority of the radiographs evaluated in the study were taken by Ms Janice Lloyd or Ms Lesley Crawford. The cases selected for the study had been under the care of Professor Neil Gorman, Dr Jane Stewart , Ms Elizabeth Munro and latterly myself. The House Surgeons have also made a considerable contribution to the care of these patients over the years. I am grateful to all staff involved for the records they have kept of the cases. In addition, the assistance of Dr Irene McCandlish and Mrs Mary Parsons in data retrieval has been greatly appreciated.

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Finally, my thanks to Professor Neil Gorman, Professor of Surgery, for his support and advice during this study.

DECLARATION

I, Laura Blackwood, do hereby declare that the work in this dissertation is original, was carried out by myself or with due acknowledgement and has not been presented for the award of a degree at any other university.

Signed:

Date: December 1993

SUMMARY

This dissertation presents the results of a retrospective study of the radiological findings in 84 cases of canine multicentric lymphoma, referred to the Department of Surgery, Glasgow University Veterinary School.

The features analysed in the study include:

- the abnormalities detected on thoracic and abdominal radiographs, and the frequency of occurrence of individual changes and combinations of changes
- the role of radiographic examination in the diagnosis of lymphoma
- the difficulties encountered in interpretation of the radiographs
- the relationship between the thoracic radiological findings and the occurrence of hypercalcaemia
- the prognostic relevance of radiological abnormalities and, in comparison, clinical staging, for the individual patient

There is little published work dealing specifically with the radiographic features of multicentric lymphoma in the dog. The results of this study are discussed in the light of the radiological studies undertaken by Ackerman and Madewell (1980) and Kene (1984).

The major conclusions are:

- the majority of cases of lymphoma have multiple radiological abnormalities
- multicentric lymphoma is not a radiological diagnosis i.e. it cannot be diagnosed on the basis of radiographic findings alone
- many of the features seen in lymphoma are non-specific, and have numerous possible causes
- cranial mediastinal disease is neither a prerequisite for, nor a disproportionately common finding in, hypercalcaemia
- the absence of radiological abnormalities may be a positive prognostic indicator, but in general radiology has no place as a prognostic indicator for the individual patient

INTRODUCTION

Malignant lymphoma is a lymphoid neoplasm arising from the solid haematopoietic organs. The lymph nodes themselves are the most common site of origin but the tumour can also arise in the liver, spleen or thymus. In 1967, Dorn and others carried out an epizootiological study and estimated an annual incidence of 24 cases of lymphoma of per 100,000 dogs. The multicentric form occurs in 84% of cases of canine lymphoma (Madewell and Theilen 1979), and is one of the most frequently occurring malignancies seen in the dog, accounting for approximately 8.5% of all canine tumours (Priester and McKay 1980). Multicentric lymphoma is characterised by bilaterally symmetrical involvement of most, if not all, superficial lymph nodes, visceral lymph nodes, spleen and liver. The remaining 16% of lymphomas are comprised of alimentary, cranial mediastinal (thymic) and extranodal forms.

Animals that present with suspected multicentric malignant lymphoma must be evaluated not only to discern the extent or grade of their primary disease but also to determine the presence of concurrent illness that may affect management and prognosis. Clinical examination must be full and thorough, and haematological and biochemical examination are routinely performed. Radiological, and increasingly ultrasonographic, examination also play an important part in the initial assessment of the case.

In common with many other neoplastic diseases, a staging system is often used to describe the extent of the disease process. This involves assessment of peripheral and internal lymph node involvement, and evaluation of the involvement of other organs. Radiography is an integral part of the staging process, allowing identification of internal disease. In addition, radiographic examination gives some indication of concurrent disease in other systems which may affect individual prognosis or the selection of cytotoxic drugs. However, the prognostic significance of this staging process is unproven.

CHAPTER 1.

LITERATURE REVIEW: RADIOLOGY IN CANINE LYMPHOMA

LITERATURE REVIEW

In veterinary literature, there is a plethora of publications on the subject of canine lymphoma. The thrust of many of these articles is the clinical and histopathological diagnosis of lymphoma, and treatment of the disease (Squire and others 1973, Madewell 1975, MacEwen and others 1977, MacEwen and others 1981, Crow 1982, Cotter 1983, Madewell 1985, Leifer and Matus 1986, Cotter and Goldstein 1987, Gorman 1989, Rosenthal 1990, Hahn and others 1992, Morris and others 1993). There is a paucity of information regarding the radiographic findings in these reports. The majority of the remaining papers are case reports of atypical lymphoproliferative disease.

The body of work which concerns itself specifically with radiographic abnormalities seen in lymphoma consists almost entirely of case reports or quiz-like short communications of interesting presentations of the disease in its less common forms (Thrall and others 1984, McCarthy and others 1988, Turnwald and others 1988, Ogilvie and others 1989, Rogers and others 1989, Shell and others 1989, Stickle and others 1991). However, Ackerman and Madewell (1980) performed a study reviewing the thoracic and abdominal radiographs of 100 canine patients with multicentric disease prior to administration of chemotherapy. Similarly, Kene (1984) reviewed the radiographic findings in 21 cats and 25 dogs with lymphoma. However, animals with cranial mediastinal, alimentary and extranodal disease were included in the latter study.

Most authors agree that radiographs of the thorax and abdomen should be taken in cases of multicentric lymphoma. However, few discuss either radiological findings or their relevance in the diagnosis and investigation of lymphoma (Squire and others 1973, Madewell 1975, MacEwen and others 1977, Leifer and Matus 1986, Page and others 1986, MacEwen and others 1987, Gorman 1989, Postorino and others 1989a, Rosenthal 1990, Hahn and others 1992). In exception to this, MacEwen and others (1981) mentioned the pulmonary patterns seen in 16 of 51 cases of lymphoma (in a chemotherapeutic trial) which had pulmonary involvement. Weller and others (1982b) recorded that the radiological findings in a series of 24 cases were similar to those recorded in 1980 by Ackerman and Madewell. Cotter (1983) and Cotter and Goldstein (1987) referred to survey radiographs of the thorax for almost all patients, but failed to comment on their findings or the reasoning behind the omission of abdominal radiographs from their patient evaluation. The animals in the latter two studies were clinically staged without the assistance of abdominal radiographs. However, Crow (1982) and Morris and others (1993) acknowledged

that survey radiographs of the thorax and abdomen are valuable in the staging of multicentric lymphoma, where radiographic examination allows appreciation of involvement of internal nodes and organs. This was supported by others including Suter and Lord (1984a,b,c) and Madewell and Theilen (1987), and these authors agreed that radiology has a role to play in diagnosis of the disease. Crow (1982) and Madewell and Theilen (1987) reiterated the features most commonly seen in the survey by Ackerman and Madewell (1980) without making further comment regarding their own findings, while Morris and others (1993) recorded the frequency of occurrence of cranial mediastinal masses, hepatomegaly and splenomegaly in 13 cases of lymphoma with bone marrow involvement.

Thus there has been relatively little work published which specifically reviews the type of radiographic changes that occur in multicentric lymphoma and the frequency with which changes are seen, singly or in combination. However, many authors discuss the findings in small numbers of patients suffering from this disease as part of larger survey groups in radiological review articles. This is especially the case in reviews of thoracic disease. The radiographic abnormalities seen in lymphoma are also described in the major radiology texts within the sections which discuss each individual abnormality which may be seen, (Suter and Lord 1984abc, Burk and Ackerman 1986ab, O'Brien 1978ab, Cantwell 1987 and McNeel 1987). However, only the studies undertaken by Ackerman and Madewell (1980) and Kene in (1984) have reviewed a number of films of patients with multicentric lymphoma and presented the information in a comprehensive and cohesive manner, in an attempt to ascertain the frequency of occurrence of the individual and combined radiographic findings of the disease. An understanding of these patterns of abnormality and an awareness of their occurrence is required if maximum information is to be obtained from survey radiographs of lymphoma patients.

Thoracic Radiology

The pulmonary patterns which arise in cases of multicentric lymphoma have been the subject of some debate. In 1970, Reif and Rhodes surveyed the thoracic radiographs of 336 dogs and described the pulmonary patterns observed in seven cases of lymphoma. In this survey, where diagnoses were subsequently confirmed histopathologically, the radiologists had detected the lesions in all cases of lymphoma, implying that a diagnosis of lymphoma could be made on the basis of thoracic radiological appearance alone. Suter and others (1974) described the typical patterns seen in association with lymphoma in a review of the radiographic appearance of pulmonary neoplasia. These descriptions of a characteristic appearance contradict Ackerman and Madewell (1980), who concluded that lymphoma was not a radiological diagnosis i.e. that the disease could not be

diagnosed on the basis of radiographic findings alone. Later in 1974, Suter and Lord described the characteristic pattern seen in lymphoma in a paper discussing the differential diagnosis of disseminated pulmonary disease of all aetiologies, but, in contradiction to the previous statement, also stated that this pattern is typical of chronic fungal disease. Myer (1980) included patients with lymphoma in a review of interstitial pulmonary disease, but did not describe the pattern seen as characteristic of this disease alone.

In keeping with the theory that lymphoma does not produce a uniquely identifiable radiographic pulmonary pattern it is also commonly mentioned as a differential diagnosis for other pulmonary conditions. Reif and Rhodes (1966) undertook a survey of the radiographic findings in older dogs and mentioned lymphoma as a differential diagnosis for the increase in linear reticular markings seen in these elderly animals. Adams and Dubeilzig (1978), Tiemessen (1989) and Dennis (1991) reported that the disseminated pattern of metastasis seen in some cases of mammary adenocarcinomata, especially the scirrhous anaplastic type, has a similar appearance to many cases of lymphoma. Similarly, Wellman and others (1985) and Shaiken and others (1991) concluded that lymphoma is the major differential diagnosis for the radiographic changes seen in malignant histiocytosis, a much rarer systemic neoplasm. Thus these authors dispute that the appearance of lymphoma is unique amongst neoplastic conditions, as implied by Suter and others (1974). Among non-neoplastic conditions, lymphoma has been listed as a differential diagnosis for age-related change (Reif and Rhodes 1966) chronic fungal conditions (Suter and Lord 1974, MacEwen and Young 1989), interstitial oedema in early left sided heart failure (Biery 1974), pulmonary infiltrate with eosinophils (Cantwell 1987) and chronic bronchitis (Dennis 1991).

The appearance of thoracic lymphadenopathy and thymic enlargement has been described in detail by Myer (1978b), Mitten (1982), Suter and Lord (1984a), and Burk and Ackerman (1986a) and lymphoma was mentioned as a frequent cause of this type of change by all authors other than Myer.

The radiographic features of pleural effusion were discussed by Lord and others (1972), Myer (1978a), Suter and Lord (1984c), Burk and Ackerman (1986a) and Cantwell (1987). Suter and Lord (1984c) included lymphoma in the discussion of the differential diagnosis of pleural effusion, referring also to concurrent cranial mediastinal or perihilar lymphadenopathy or pulmonary pathology. The other authors did not expand as to the potential causes of pleural fluid, except to describe the radiographic appearance created by an exudative rather than a transudative effusion. Thrall (1983) and Noone (1985), however, concluded that

lymphoproliferative neoplasia is the most common neoplastic cause of pleural effusion.

In 1980, Ackerman and Madewell reviewed the thoracic radiographic findings in 100 cases of multicentric lymphoma. Kene, in 1984, reviewed the thoracic radiographs of 24 cases of canine lymphoma, without specifying the anatomic type. However, as more than 80% of cases of canine lymphoma present in the multicentric form, it is likely that most of these cases were of this type. Thoracic lymphadenopathy and pulmonary infiltration were frequent findings in the reviews undertaken by these authors, which are discussed in depth later in the text.

Abdominal Radiology

Sublumbar lymphadenopathy has been reported to occur secondary to many conditions, and lymphoma is listed as a major differential diagnosis for enlargement of the sublumbar nodes by Burk and Ackerman (1986b) and Hammer and Couto (1991). The radiographic appearance was described by Root (1974a), O'Brien (1978b) and Burk and Ackerman (1986b).

Multicentric lymphoma has been listed as a possible cause of generalised hepatomegaly by many authors, including Ackerman and Silverman (1977), O'Brien (1978c), Burk and Ackerman (1986), Evans (1987) and McNeel (1987). Root (1974ab) and Suter (1982) described in detail the radiographic appearance of hepatomegaly and discussed the various factors which can influence this. However, neither of these papers included lymphoma specifically in their list of differential diagnoses.

Couto (1985) believes that haematopoietic neoplasms are probably the commonest cause of splenomegaly in small animals. Again, the radiographic manifestations of splenomegaly are described in a number of texts and papers including Root (1974ab), Ackerman and Silverman (1978), O'Brien (1978c), Burk and Ackerman (1986b) and McNeel (1987). The latter three texts also list lymphosarcoma as a differential diagnosis in this type of change.

O'Brien (1978c) reported that renal enlargement was commonly seen in association with hepatomegaly or hepatosplenomegaly in cases of lymphoma, but this is not substantiated by other studies (Ackerman and Madewell 1980, Kene 1984).

Hepatomegaly, splenomegaly and sublumbar lymphadenopathy were frequent findings in the retrospective studies undertaken by Ackerman and Madewell (1980)

and Kene (1984). The findings of these authors will be discussed in greater detail within the relevant sections of the text.

Hypercalcaemia and Its Relationship to Radiological Abnormalities

Hypercalcaemia is a relatively common paraneoplastic syndrome in animals with lymphoproliferative disease, reported to occur in between 10% and 33% of patients (MacEwen and Siegel 1977, Couto 1989, Meuten and Armstrong 1989, Kruth and Carter 1990). This syndrome is commonly seen in man, in association with a number of neoplasms (Gardner 1968, Brown 1981). In man, it may be associated with direct bone destruction secondary to bone metastases (MacEwen and Siegel 1977). In contrast, this is rarely seen in the dog (MacEwen and Siegel 1977, Elliott and others 1991) where humoral factors are implicated in hypercalcaemia associated with lymphoma (Norrdin and Powers 1983, Weir and others 1983). In this disease, extensive bone marrow involvement may also result in hypercalcaemia (Chew and Meuten 1982) and it has been suggested that there is a locally acting factor which causes bone resorption and hypercalcaemia (Meuten and others 1983).

Several authors have associated hypercalcaemia of malignancy with cranial mediastinal lymphoproliferative disease (MacEwen and others 1977, Chew and Meuten 1982, Wootton and Pearson 1988, Meuten and Armstrong 1989). However, this association was disputed by Weller and others (1982b) and Elliott and others (1991). The diagnosis of cranial mediastinal disease was based on radiographic evaluation in these studies. However, the small numbers of patients involved in each group preclude accurate assessment of the relationship between cranial mediastinal disease and the frequency of occurrence of hypercalcaemia.

CHAPTER 2.

MATERIALS AND METHODS

Population Data

The 84 cases reviewed in this study were presented to the University of Glasgow Veterinary Hospital between 1986 and 1993, having been referred by practising veterinarians. The study group represents a number of non-consecutive cases of multicentric lymphoma. These animals were identified using both the histopathology database and the clinical records database. Dogs that suffered from solid lymphoma without multicentric involvement were excluded from the survey. In addition, animals for which inadequate clinical details were available were excluded from the study, as were those that had not been radiographed. Cases where the radiographs were of inadequate technical quality were also eliminated from the review. Patient positioning faults which could interfere with interpretation were noted and if these faults precluded accurate assessment of the selected parameters, the films were excluded from the study.

The group of 84 cases selected for this study was composed of 39 entire male dogs, 2 castrated male dogs, 24 entire female bitches and 19 spayed bitches: there were 41 male and 43 female patients. This data is presented in Figure 2.1.

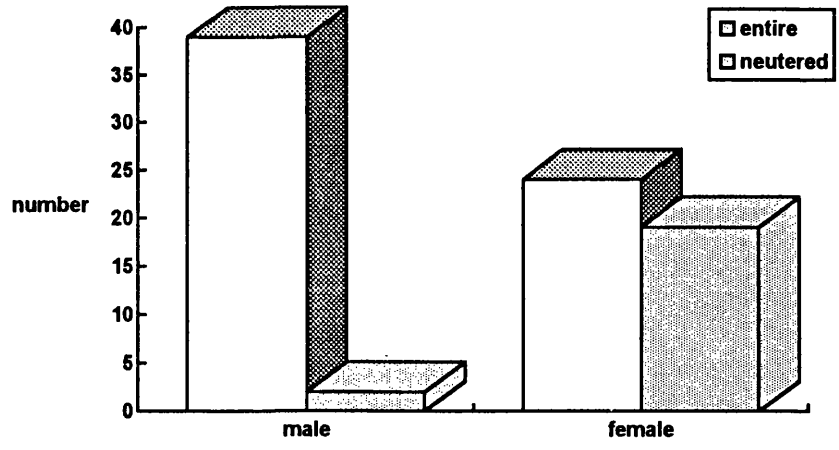


Figure 2.1. Distribution of sexes in 84 cases of lymphoma.

Twenty six pure breeds were represented: this data is presented in Table 2.1. (Percentages are given for the more frequently represented breeds only.) In addition to these purebred dogs, there were 18 crossbred animals. The boxer appeared subjectively to be over-represented relative to the hospital population, but this cannot be substantiated as the distribution of breeds within the general hospital population during the period of study has not been analysed.

BREED	NUMBER (% of 84)	BREED	NUMBER
Crossbreed	18(21%)	Old English Sheepdog	2
Labrador	13(16%)	Greyhound	1
Retriever	6(7%)	English Springer Spaniel	1
German Shepherd Dog	6(7%)	Lhaso Apso	1
Boxer	5(6%)	Gordon Setter	1
Irish Setter	4	Scottish Terrier	1
Rottweiller	3	Tibetan Terrier	1
Bull Mastiff	3	Miniature Poodle	1
Doberman Pinscher	2	Corgi	1
West Highland White Terrier	2	Rough Collie	1
King Charles Cavalier Spaniel	2	Shetland Sheepdog	1
Great Dane	2	Jack Russell Terrier	1
Airedale	2	Beagle	1
Border Collie	2		

Table 2.1: Breed distribution of 84 cases of multicentric lymphoma.

The mean age of the patients at presentation was 6.95 years. (range two years to 16.5 years). Figure 2.2 shows the age distribution of the cases studied. Fifty seven percent of patients were between five and ten years of age at time of presentation with lymphoma.

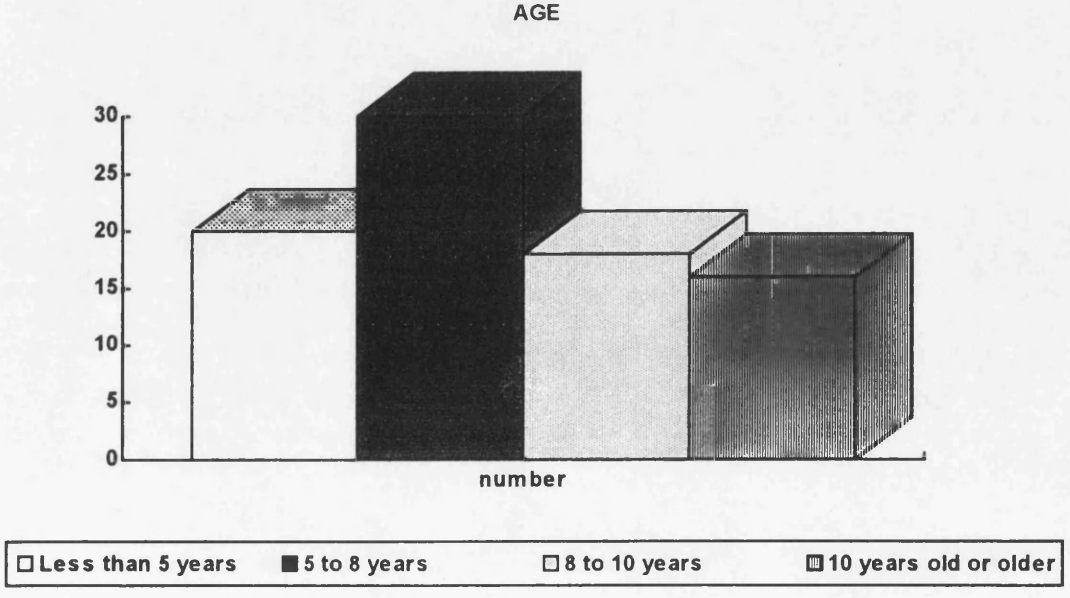


Figure 2.2: Ages of patients with multicentric lymphoma at presentation.

Patient Evaluation

All patients were submitted to a clinical examination. Routine haematological and biochemical evaluations were carried out on every patient and comprised a complete blood count, cytological examination of blood smears and biochemical assessment of plasma levels of urea, creatinine, phosphate, calcium, sodium, potassium, alkaline phosphatase, aspartate transaminase, alanine transferase, cholesterol, glucose, total protein, albumin and globulin. In addition, bone marrow aspiration was carried out in some cases. Urinalysis results were available in a minority of cases.

Survey radiographs of the chest and abdomen were taken for almost all patients: thoracic radiographs only were available for five patients which had presented early in the chosen period. A routine electrocardiogram (lead II) and M-mode ultrasonographic measurement of fractional shortening were carried out in addition to thoracic radiography where anthracycline agents were to be used. The diagnosis of lymphoma was confirmed by histopathology or cytology. Tissue for histopathology was obtained by excisional biopsy, usually of one of the popliteal lymph nodes (Fossum 1990). Tissue samples for cytological examination were obtained by fine needle aspirate, usually from one of the prescapular lymph nodes. A 25 gauge, 3/4 inch needle and 10ml syringe were used to obtain the aspirate (White 1991).

Plain films of the thorax and abdomen, taken at first presentation, were evaluated for the 84 selected dogs with lymphoma. All films in the study were taken prior to initiation of chemotherapy. Lateral thoracic views were available for all 84 cases. These were evaluated for evidence of suprasternal, cranial mediastinal, and tracheobronchial lymphadenopathy, thymic enlargement, pleural disease and pulmonary infiltration. Where available dorsoventral views were examined to evaluate mediastinal widening as well as the features above. No special horizontal beam projections or contrast studies were available. Lymph node size was analysed subjectively and graded on a scale of 0 to 3, where 0 refers to no enlargement, 1 refers to slight detectable enlargement, 2 to moderate and 3 to marked enlargement. Where it was impossible to evaluate node size, for example in the presence of pleural effusion, then this difficulty and the reason it occurred was noted. The presence or absence of pulmonary change was used as a primary screen in this study. The films with pulmonary change were subsequently re-examined and the pulmonary changes categorised by the author.

Lateral abdominal views were available for 79 of the 84 cases. Two lateral views were taken of some of the giant breed dogs to allow adequate assessment of both

cranial and caudal abdominal organs. Specifically, the abdomen was examined for hepatomegaly, splenomegaly, sublumbar lymphadenopathy and ascites. Again, the sublumbar node size was graded on a scale of 0 to 3.

The radiographs were examined and the presence or absence of the changes outlined above were noted. Lymph node enlargement was quantified for every film, and the patterns of pulmonary abnormality defined. In addition, any other radiographic abnormalities detected by the viewer during examination of the radiographs were recorded.

The radiographic interpretations were carried out independently by three radiologists. Each interpreter studied the films alone and was unaware of the findings of the other viewers. This served not only as a quality control but also to highlight the particular aspects of interpretation which pose problems in this type of case. Where there was a discrepancy in the recorded findings, the films were reviewed by the author and one of the other viewers and a final decision made, as well as an attempt made to quantify the factors which had lead to the anomalous results. All three viewers were aware that the radiographs were of patients suffering from multicentric lymphoma.

Clinical Staging

It was hoped that the study would also provide some information regarding the prognostic implications of the radiographic findings. In an attempt to make this exercise worthwhile, each patient was retrospectively staged according to a modification of the W.H.O. staging system (Table 2.2, page 12). This staging system is very similar to that defined for the W.H.O. by Owen (1980), and was selected because it offers clearer description of the categories of subdivision. The actual clinical stages of individual patients are identical using either system.

Stage	Criteria
I	Involvement of one lymph node, contiguous nodes or another single site such as the thymus.
II	Involvement of two or more non-contiguous nodes on the same side of the diaphragm.
III	Multiple sites on both sides of the diaphragm without splenomegaly.
IV	Multiple sites on both sides of the diaphragm with hepatomegaly and /or splenomegaly.
V	Multiple sites including non-lymphoid tissues, bone marrow, skin or the central nervous system.

Table 2.2: Modified staging system for canine lymphoma (Gorman 1991).

The 84 animals were staged clinically using this version of the W.H.O. staging system, and divided further into subgroups (a) and (b). These refer to (a) the absence of systemic signs and (b) their presence. (In the five cases where abdominal radiographs were not available to allow assessment of abdominal organs, staging was based on the recorded clinical stage at presentation, the recorded findings of the clinical examination and assessment of the cranial abdomen on the periphery of the thoracic radiographs.) Almost all animals presented with multicentric lymphadenopathy, with only two cases having regional lymphadenopathy at initial clinical examination. The majority of the animals presented with relatively advanced disease, particularly in the early part of the period studied. This may reflect lack of awareness of the disease and treatment options within the referring veterinary practices at this time. Fifty five (65%) of the 84 animals showed systemic signs of disease at the time of presentation. The distribution of the cases within stages is given below (Table 2.3).

Clinical Stage	Number of Cases		
	(a)	(b)	Total
II	0	2	2
III	10	10	20
IV	16	19	35
V	3	24	27
Total	29	55	84

Table 2.3: Modified W.H.O. staging of 84 cases of lymphoma.

Serum Calcium Assessment

The serum calcium levels on presentation were recorded and corrected relative to albumin levels using the formula stated below (Meuten and others 1982) These results were based on blood samples taken prior to fluid therapy or drug administration, on the day of or the day before radiographic examination. Analysis was carried out using an atomic absorption spectrophotometer (Instrumentation Laboratory, Warrington: model IL 2517.)

Adjusted calcium(mg/dl) = 3.5 - albumin(g/dl) + measured calcium(mg/dl)

The units used in the University of Glasgow Veterinary Hospital for calcium are mmol/l: these are converted into mg/dl by multiplying by 4. The units for albumin are g/l: these are converted into g/dl by dividing by a factor of 10 (Meuten and Armstrong 1989.)

Statistical Analysis

The statistical analyses of the influence of radiological findings and clinical stage on survival times presented in Chapter 6 and Appendix 2 were carried out using *Excel 4.0* (Microsoft) to create spreadsheets, which were then exported into *Minitab 7.1* (Minitab Inc) for regressional analysis. Statistical significance was set at the 95% level ($p<0.05$).

Discussion of Population

Mean ages of seven or eight years are reported for lymphoma cases in a number of studies (Madewell 1975, MacEwen and others 1981, MacEwen and others 1987, Postorino and others 1989a). Most dogs were middle-aged, but all authors report a wide range of ages comparable with that in the present study, where dogs from two to 16.5 years old were affected. No sex predilection has been reported (Dorn and others 1967, Madewell 1975, MacEwen and others 1977, Weller and others 1982a, MacEwen and others 1987) and the sex distribution of this group supports these findings.

Various studies have suggested certain breeds may be preferentially affected: these breeds include the boxer, German shepherd dog, beagle, basset hound, golden retriever, Saint Bernard, old English sheepdog, hunting breeds and the Scottish terrier (Dorn and others 1967, Priester 1967, MacEwen and others 1977, Priester and McKay 1980, Cotter 1983). There may be a familial incidence of lymphoma in bull mastiffs (Onions 1984). Other workers have found no obvious breed

predilection (Postorino and others 1989a), and the variety of breeds presented in the literature as having an increased frequency of disease may in some cases reflect artefactual findings due to regional variations in breed populations and relatively small case numbers. Most of these findings are based on American studies and therefore may be of less relevance in the United Kingdom. The boxer is repeatedly reported to suffer from an increased risk of lymphoma and is apparently over-represented in the current study. This relatively high risk of this disease in the boxer compared to other breeds was evaluated in 1967 by Priester.

CHAPTER 3.

THORACIC RADIOLOGICAL ABNORMALITIES IN DOGS WITH MULTICENTRIC LYMPHOMA

THORACIC RADIOLOGICAL FINDINGS: RESULTS

The radiological findings of the review of 84 sets of thoracic radiographs of patients with multicentric lymphoma are given below (Table 3.1). The individual findings are listed in Appendix 1.a. (pages 107-110).

Radiological abnormality	Number affected (%)	Size (Score) 1	2	3
Suprasternal lymphadenopathy	34 (40%)	20	12	2
Tracheobronchial lymphadenopathy	28 (33%)	16	9	3
Cranial mediastinal lymphadenopathy	22 (26%)			
Thymic infiltration	6 (7%)			
Pulmonary infiltration	31 (37%)			
Pleural change	19 (23%)			

Table 3.1: The thoracic radiological findings on review of 84 lymphoma patients.

In 20 of the 84 (24%) cases, no thoracic abnormalities were detected. Twenty three (27%) patients had a single abnormality detected. Forty one (49%) animals showed multiple thoracic abnormalities.

Lymph Node Enlargement

Suprasternal lymphadenopathy was the most common radiographic abnormality, being seen in 34 of the 84 (40%) selected cases (Figure 3.1, page 18 and Figure 3.3b, page 20). These cases included 20 where the node enlargement received a score of 1, 12 cases where the score was 2 and only 2 cases where the score was 3. In 28 of the 84 (33%) cases, the forelimbs were insufficiently drawn forward and thus to some extent obscured the suprasternal nodes. However, in 13 of these 28 cases suprasternal lymphadenopathy was detected. Films in which positioning was so poor as to completely obscure this area were excluded from the study. It was unusual to see suprasternal lymphadenopathy as a solitary change (7 cases, i.e. approximately 8%).

Tracheobronchial lymphadenopathy was seen in 28 of the 84 (33%) cases. These cases included 16 where the node enlargement received a score of 1, nine where the score given was 2 and three where the score was 3. Only one animal showed this

feature as a solitary thoracic change. Eighteen of the 84 (21%) animals had concurrent tracheobronchial and suprasternal lymphadenopathy. The changes seen when the tracheobronchial nodes were enlarged are summarised in Table 3.2

Tracheobronchial lymphadenopathy score	Number affected	Tracheal deviation		Poorly marginated perihilar density	Marginated perihilar mass/masses
		Dorsal	Ventral		
3	3	2	3	1	2
2	9	1	1	8	3
1	16	0	1	15	2

Table 3.2: Radiographic features of tracheobronchial lymphadenopathy seen in lymphoma series.

Of the three animals with marked tracheobronchial lymphadenopathy (score 3), one had a marked but poorly marginated increase in density in the perihilar region and two had masses with identifiable margins, which were clearly visible if not sharp at all points (Figure 3.1, page 18). The animals with moderate lymphadenopathy generally showed a poorly marginated increase in density in this area, though in one case only the middle tracheobronchial node was obviously enlarged and had distinct margins. In two of the remaining cases with moderate node enlargement, there was an overall increase in density in this area accompanied by distinct margins of particular nodes. The distinct nodes were the right tracheobronchial node in one case and the middle tracheobronchial node in the other. In the latter case, in addition to slight dorsal displacement of the trachea over the node there was caudal displacement of the right mainstem bronchus. In the group of animals with slight change, most showed a rather vague increase in density in the perihilar region, but in one case this was accompanied by two small distinct densities in the positions of the right and left bronchial nodes. Another showed a single small fairly distinct mass dorsal to the bifurcation, representing the middle tracheobronchial node. Tracheal deviation was commoner when the nodes were larger. The patterns of change seen are illustrated in photographic and diagrammatic form (Figure 3.1, page 18 and Figure 3.2, page 19).

Cranial mediastinal lymphadenopathy was seen in 22 of the 84 (26%) patients (Figure 3.3a, page 20). This abnormality was never recorded as a solitary change. In 11 of these cases, there was concurrent enlargement of both suprasternal and tracheobronchial nodes. Two of these cases with enlargement of all three thoracic nodes also had radiographic evidence of thymic enlargement.

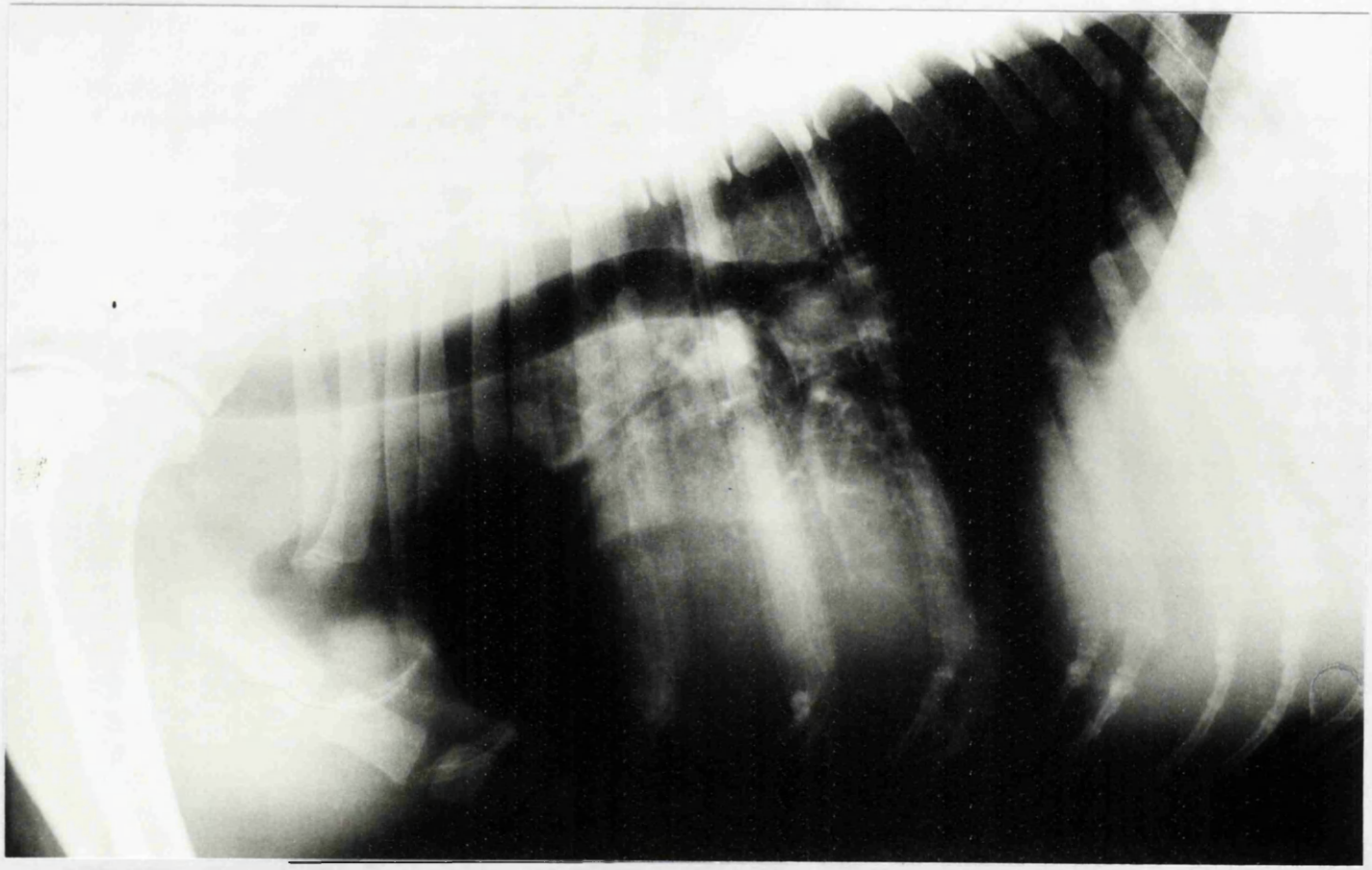
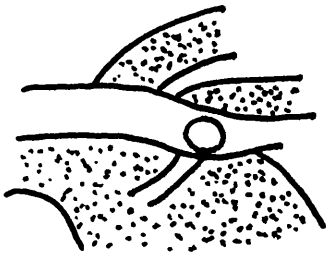
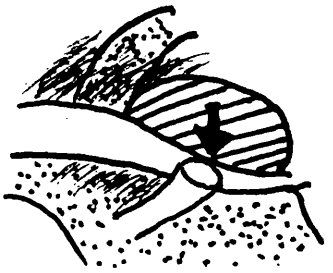


Figure 3.1: Lateral view of the thorax of a dog with multicentric lymphoma showing moderate enlargement of the suprasternal nodes and marked enlargement of the tracheobronchial nodes, causing tracheal deviation.

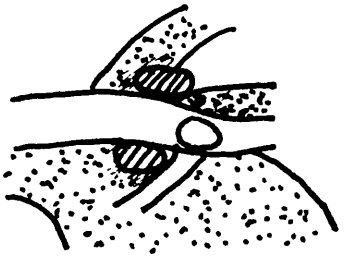


A. Hilar region of a normal dog.

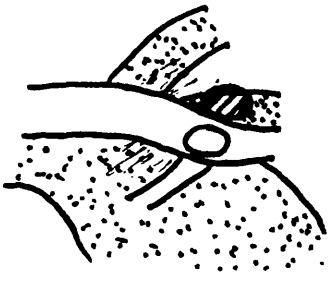


B. Ill-defined increase in density in the perihilar region accompanied by a moderately enlarged, marginated middle tracheobronchial node which is displacing the trachea ventrally (score 2).

C. Ill-defined increase in density in the perihilar region accompanied by distinct right tracheobronchial node, displacing the trachea slightly dorsally and the right mainstem bronchus caudally (score 2).



D. Small distinct soft tissue densities representing slightly enlarged right and left tracheobronchial nodes (score 1).



E. Single small soft tissue mass representing the slightly enlarged middle tracheobronchial node (score 1).

Figure 3.2: Diagrammatic representations of some patterns of tracheobronchial lymphadenopathy seen in lymphoma.

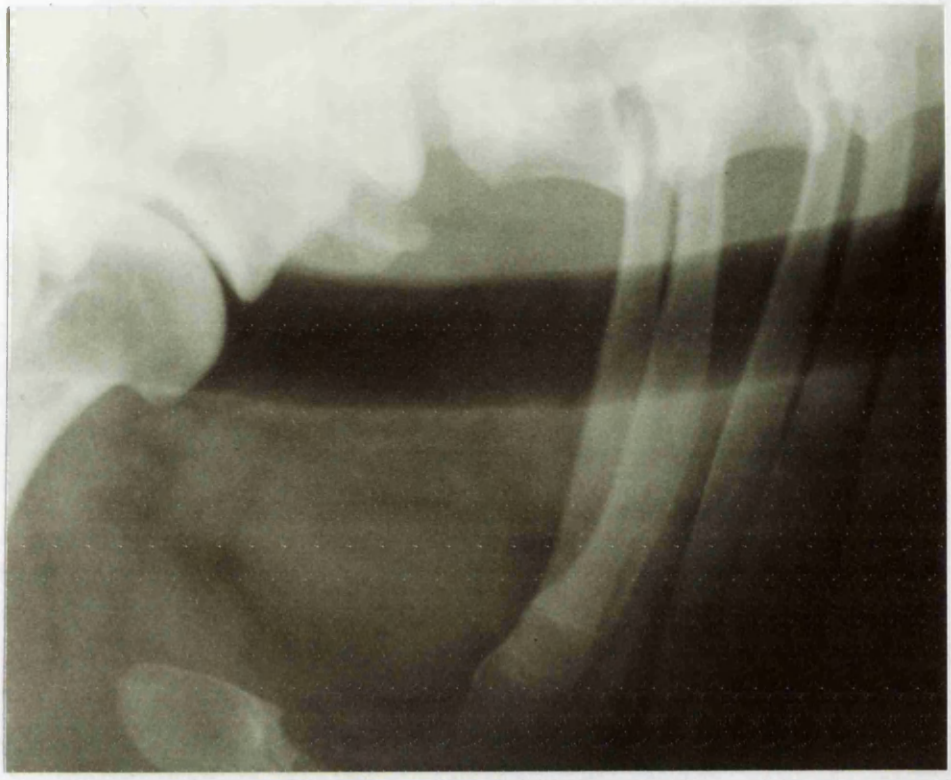


Figure 3.3a: Lateral view of the thoracic inlet and cranial thorax of a dog with multicentric lymphoma, illustrating enlargement of the cranial mediastinal lymph nodes, seen opposite the first rib and ventral to the tracheal shadow.

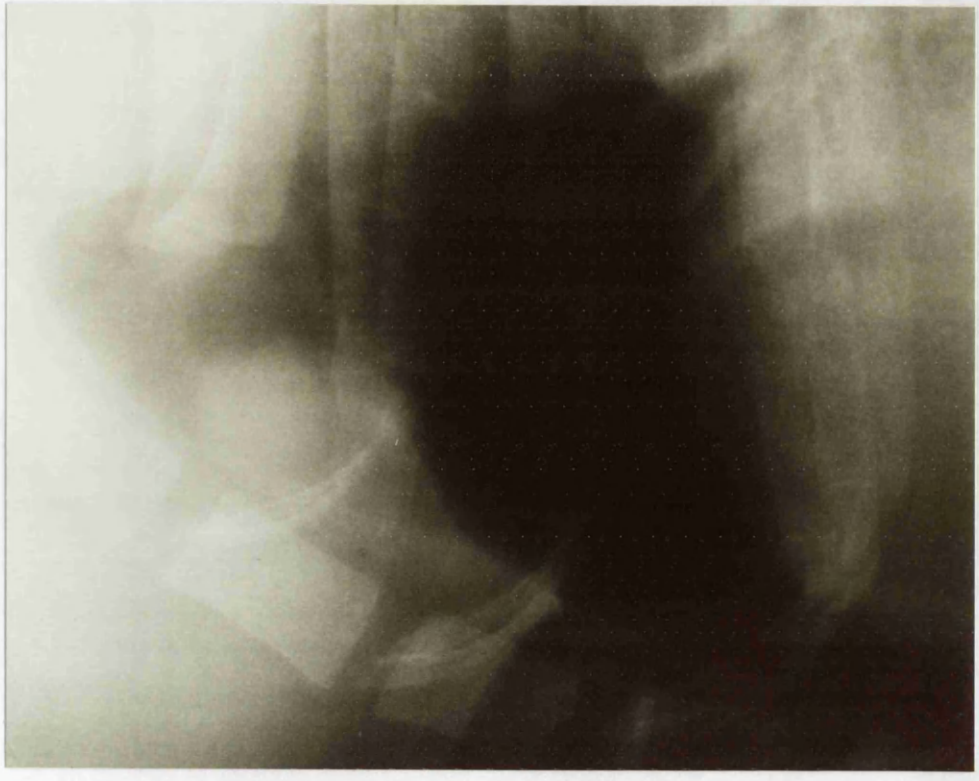


Figure 3.3b: Lateral thoracic view of a lymphoma patient showing enlarged suprasternal lymph nodes (close up).

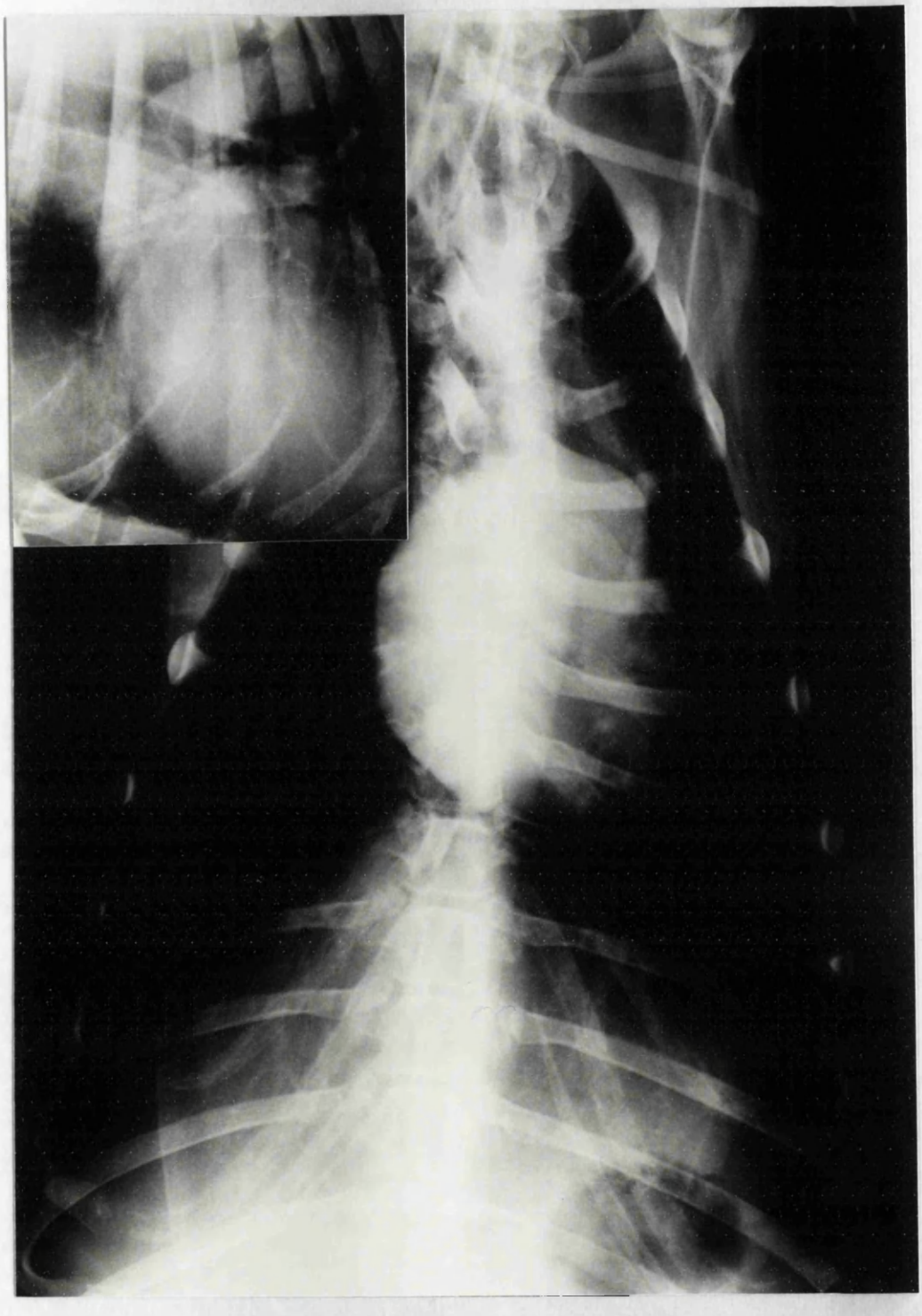


Figure 3.4: Dorsoventral view of the thorax of a dog with thymic enlargenet (inset shows the appearance of the thymus on the lateral view).

Thymic Enlargement

Enlargement of the thymus gland was recorded in only six of the 84 (approximately 7%) cases reviewed (Figure 3.4, page 21). It was the only thoracic abnormality seen in one case. The other patients had various combinations of thoracic lymphadenopathy as well as thymic enlargement. No animal had thymic enlargement and tracheobronchial node enlargement without involvement of both the suprasternal and cranial mediastinal nodes i.e. the other cranial mediastinal lymphoid organs. There were no cases of detectable thymic enlargement and pleural effusion.

Pulmonary Infiltration

Abnormal pulmonary infiltration was detected in 31 (37%) of the 84 patients. Most of these patients showed a micronodular or reticular interstitial pattern, or a combination of both. A few animals also showed alveolar infiltration and in several cases peribronchial shadows were also seen. Pulmonary infiltration was seen as the sole abnormality in seven of the patients. Most of the animals with radiological evidence of pulmonary infiltration also had thoracic lymphadenopathy: 22 of the 31 affected dogs had concurrent enlargement of at least one of the thoracic nodes.

The abnormal pulmonary patterns seen are summarised in the Table 3.3. In four cases, the presence of pleural effusion led to lung collapse which precluded the assessment of pulmonary pattern. In the remaining three of the seven animals with pleural fluid, the pulmonary pattern was visible and no abnormalities were detected.

Observed pulmonary pattern	Number affected
Micronodular infiltrate	14
Micronodular and alveolar infiltrate	2
Reticular markings	1
Reticulonodular pattern: linear markings predominant	7
Reticulonodular pattern: micronodular pattern predominant	4
Truly mixed reticulonodular pattern	3
Total number	31

Table 3.3: Classification of abnormal interstitial patterns seen in lymphoma patients.

In a total of 16 animals, the disseminated interstitial pattern was defined as micronodular. Of the remainder, there were 14 cases where a mixed reticulonodular interstitial infiltrate was identified, and one animal recorded to have an increase in reticular markings only. In six of the cases showing micronodular change, this pattern was described as marked. This means that the nodules were readily identifiable and more prominent than would have been expected as a result of, for example, innocuous senescent change. In one case, which also had alveolar change, the interstital nodules also appeared to coalesce, but this may have been due to the superimposed alveolar infiltrate. In four cases, the micronodular pattern was described as grainy or sandy, implying the presence of many very small rather irregular nodules. In addition to the features mentioned above, eight of the 31 animals had prominent peribronchial markings. In two cases, these manifest as markedly thickened peribronchial cuffs and in six cases thinner but prominent peribronchial shadows were seen. Four cases had distinct linear opacities thought to be due to dilated lymphatics: these were longer and more distinct than the non-vascular curvilinear interstitial markings but not as dense as calcified interlobar fissures. These linear densities were not in the anatomical locations of interlobar fissures.

Examples of the patterns of pulmonary change seen are illustrated in Figures 3.5, 3.6 and 3.7. on pages 24, 25 and 26.

A solitary lesion was seen within the pulmonary parenchyma of one dog within the study group. This mass remained unchanged throughout the course of the dog's treatment and did not reduce in size when the dog went into remission. The mass was well circumscribed, roughly spherical, approximately 4cm in diameter, and of homogeneous soft tissue density with sharp margins. It was situated within the pulmonary parenchyma of the right diaphragmatic lobe, and there were no air bronchograms visible within it (Figure 3.8, page 27). Unfortunately, permission for post-mortem was refused when the dog was euthanased, so no final diagnosis was made as to the nature of the mass. It is most likely that this mass was a slow growing primary pulmonary tumour and for this reason the patient has not been included in the group of animals with pulmonary infiltration.

Senescent pulmonary change was seen in many of the cases examined. This consisted of thin peribronchial cuffs, tracheal and bronchial calcification, and non-vascular curvilinear and unstructured interstitial markings.

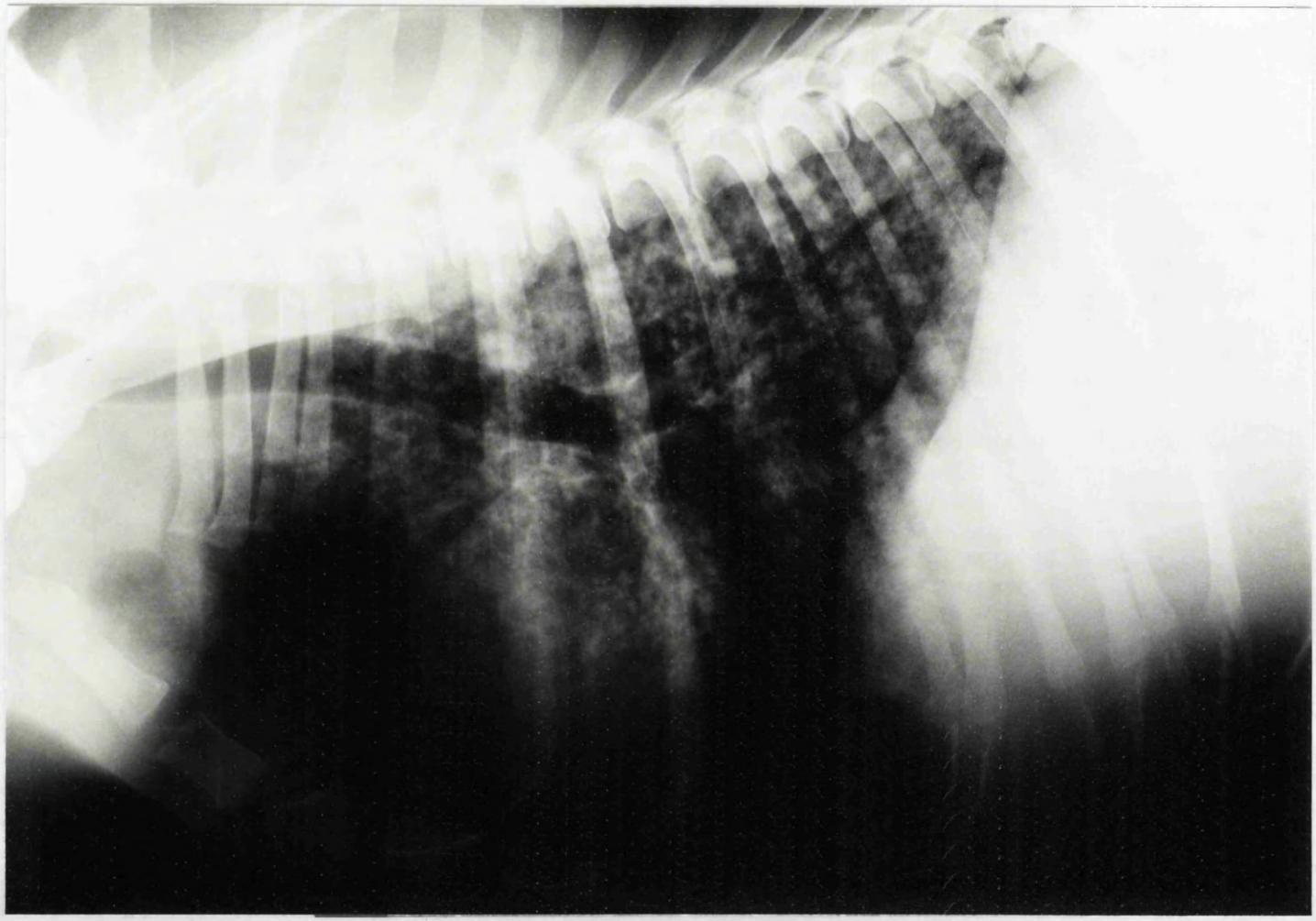


Figure 3.5: Lateral thoracic view of a dog with multicentric lymphoma, showing diffuse alveolar-interstitial markings and thick peribronchial cuffs.

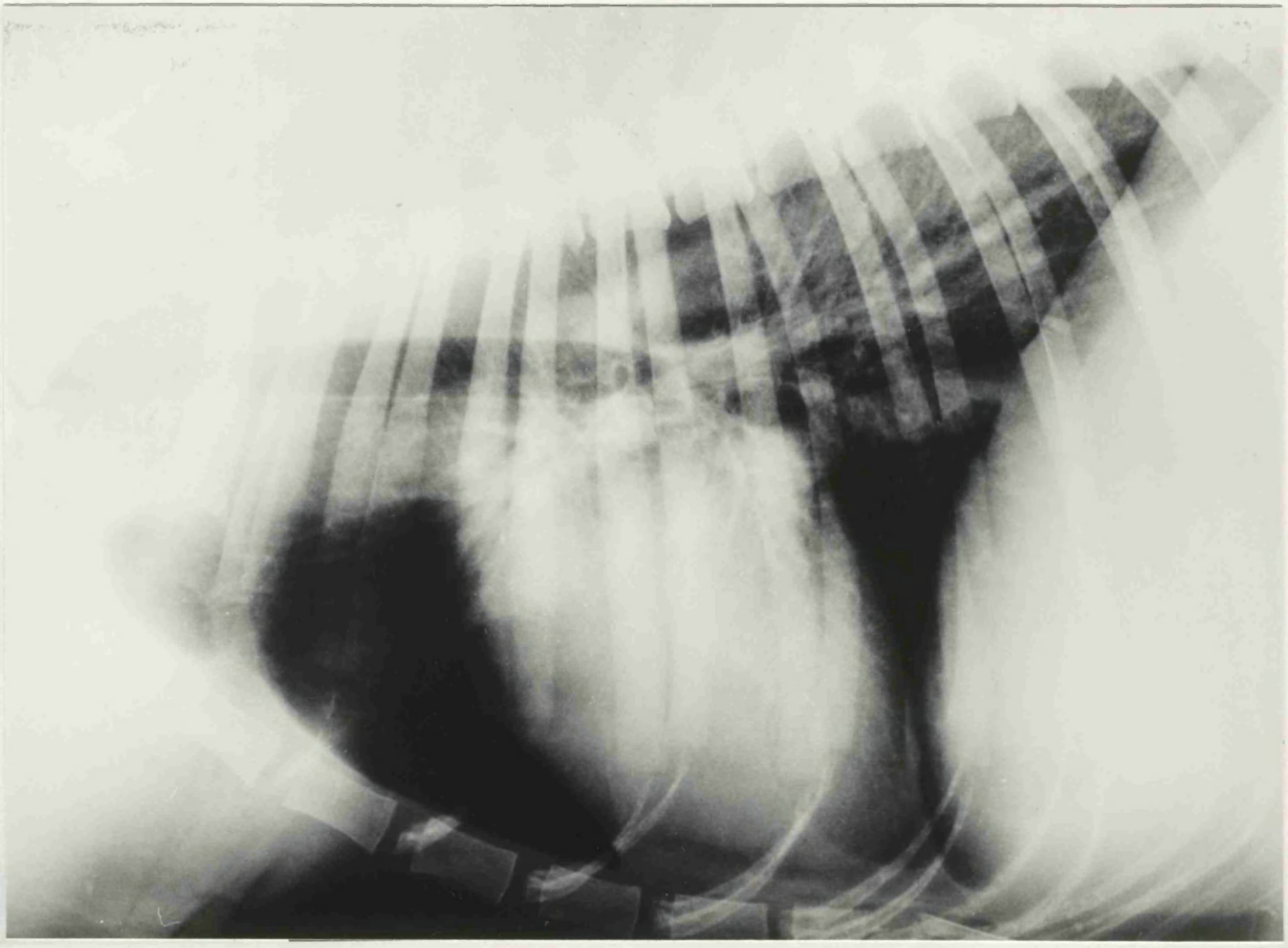


Figure 3.6: Lateral view of the thorax of a dog with lymphoma, showing a very fine "grainy" disseminated micronodular interstitial pattern.

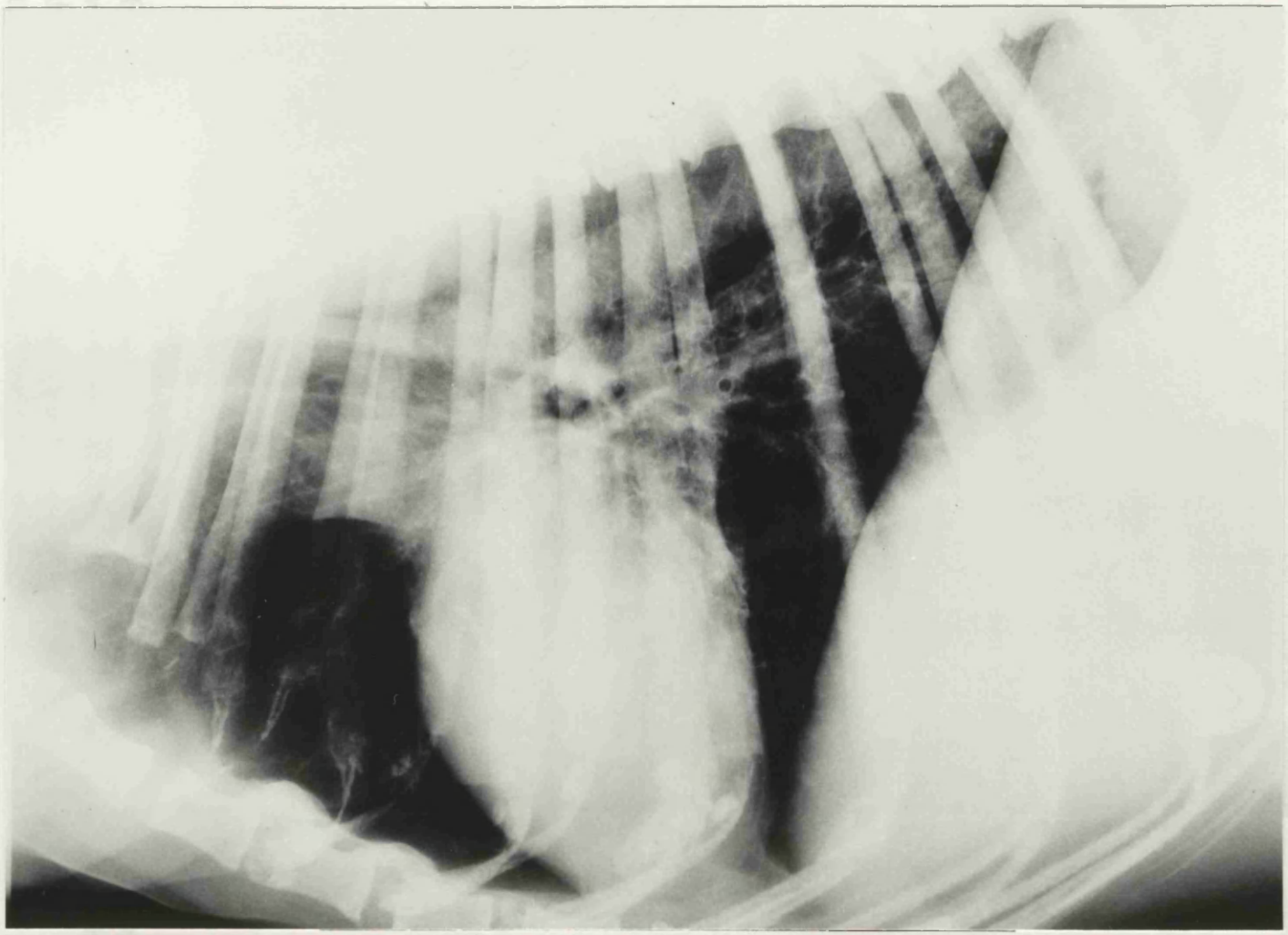


Figure 3.7: Lateral thoracic radiograph of a dog with lymphoma, showing a diffuse reticulonodular infiltrate in which reticular markings predominate. The cardiac shadow is narrowed, suggesting hypovolaemia.

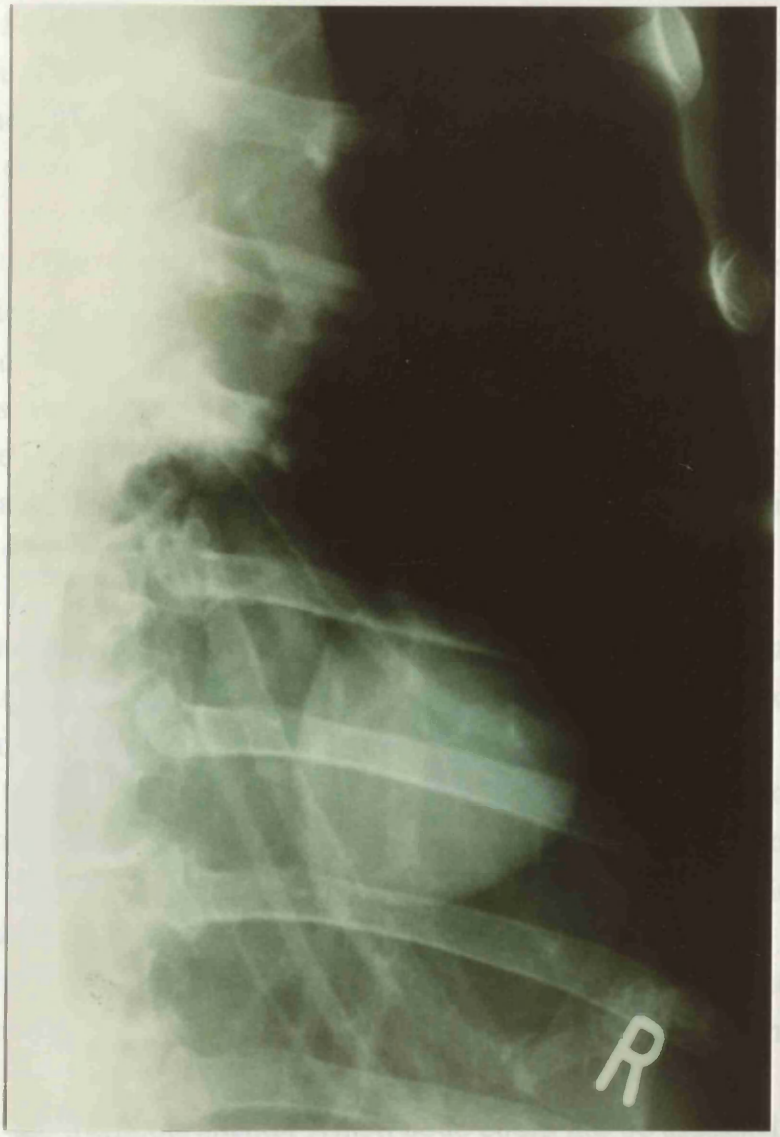


Figure 3.8: Dorsoventral radiograph (in close up) of the thorax of a dog with multicentric lymphoma, showing a soft tissue mass within the right diaphragmatic lung lobe (thought to be a slow growing primary lung tumour).

Pleural Change

Pleural change was seen in 19 (23%) of the 84 cases examined. In seven cases, a pleural effusion was seen. None of the animals which had pleural effusion were profoundly hypoalbuminaemic (range 21-38g/dl). In the remaining 12 cases, interlobar fissures were visible due to pleural thickening or the presence of a very small amount of fluid. The most commonly visible interlobar fissures were those between the right middle lobe and the diaphragmatic lobe or between the caudal part of the left cranial lobe and diaphragmatic lobe. Of the seven patients with pleural change as the only recorded thoracic abnormality, four had effusions and the remaining three had only pleural thickening. Effusions detracted from interpretation of other radiographic features of the disease, often making detection of lymphadenopathy or thymic enlargement difficult or impossible. In most of these cases the degree of atelectasis of the lungs was such that subtle interstitial changes were not detectable. The radiographs of the animals with pleural effusion were re-examined and the problems created by the presence of fluid are summarised in Table 3.4. (page 29).

The suprasternal and cranial mediastinal nodes were the most commonly obscured. Identification of thymic enlargement was also precluded in five of the seven cases. In the remaining two cases, the volume of effusion was small and the area just cranial to the cardiac shadow was not obscured, so it was decided that thymic enlargement would have been detectable if present. In the two cases (1 and 4) where the suprasternal node was partially obscured, the node was massively enlarged (score 3) and was thus visible despite the presence of a moderate amount of fluid. In patient 1, the cranial mediastinal node was also markedly enlarged and the dorsal margins of this soft tissue mass could be visualised on the lateral view.

In one case the tracheobronchial lymph node could not be assessed. In this case the distribution of fluid was atypical, and the volume was greater than in the other cases. There was an accumulation of fluid mainly on the right hand side, causing complete collapse of the right middle lung lobe and partial collapse of the right cranial lobe (Figure 3.9, page 30). A small amount of fluid outlined the interlobar fissures on the left, and separated the lungs from the thoracic wall. On the lateral view, much fluid was seen dorsally between the right cranial and diaphragmatic lobes and also over the cardiac shadow in the site of the right middle lobe. A smaller amount was seen extending cranioventrally. In the other cases fluid tended to accumulate ventral to the lung lobes, obscuring the cardiac apex and cranial mediastinal structures. In the case of patient 2 there was only a very small amount of fluid present and the cranial mediastinal structures were visible.

	Radiographic Feature Obscured				
Patient	Suprasternal lymph node	Cranial mediastinal lymph node	Tracheobronchial lymph node	Thymus	Pulmonary pattern
1	Partially	Partially	No	Yes	No
2	No	No	No	No	No
3	Yes	Yes	No	Yes	Yes
4	Partially	Yes	No	Yes	Yes
5	Yes	Yes	No	Yes	Yes
6	Yes	Yes	Yes	Yes	Yes
7	Yes	Yes	No	No	No

Table 3.4: The problems in the detection of thoracic change in lymphoma patients with pleural effusion.

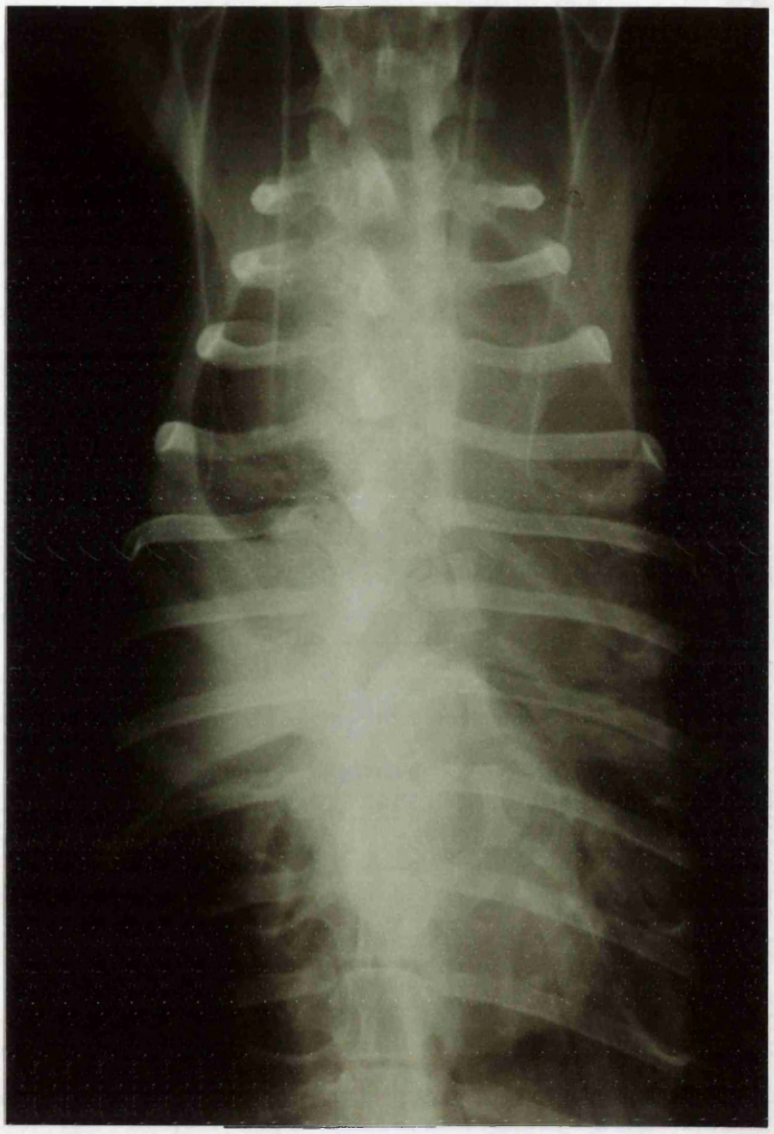


Figure 3.9: Dorsoventral view of the thorax of a dog with multicentric lymphoma. There is bilateral pleural effusion, and the right hand side is preferentially affected. The right middle lung lobe has collapsed.

Other Radiographic Findings

Five of the dogs were noted to be hypovolaemic, based on radiological findings of microcardia, reduced prominence of pulmonary vessels and/or narrowing of the great vessels. Only one animal had cardiomegaly. In many cases small amounts of air were seen in the thoracic oesophagus as result of sedation, but in one case there was marked dilation along the whole length of the thoracic oesophagus.

A number of animals had ventral spondylosis affecting the thoracic vertebrae, degenerative changes of the elbows or shoulders seen incidentally at the cranial edge of the film, and sternebral degenerative changes. These findings reflected the age of the survey population.

DISCUSSION OF THORACIC RADIOLOGICAL FINDINGS

MEDIASTINAL ABNORMALITIES

The structures within the mediastinum analysed specifically in this study were the suprasternal lymph nodes, the cranial mediastinal lymph nodes, tracheobronchial nodes and the thymus.

The sternal or suprasternal lymph nodes are usually represented by a single node on each side. They are very occasionally absent, and rarely a single node or multiple nodes are present. The mediastinal nodes also vary in both number and shape between individuals. In the dog (unlike other species) these nodes are confined to the cranial (or precardial) mediastinum, where they take up position to the left or right of midline. On the left hand side, between one and six nodes lie along the cranial vena cava, left subclavian and costocervical arteries. One large node is usually located opposite the first intercostal space. On the right hand side, two or three (or occasionally up to six) lymph nodes are found. The most constant and largest of these is seen between the right costocervical vein and the cranial vena cava. Smaller nodes are found in other sites but these are rarely radiographically detectable even if enlarged.

The tracheobronchial nodes are a group of nodes comprising those nodes which lie on the primary bronchi at the tracheal bifurcation. The left and right tracheobronchial nodes lie on the lateral surface of the respective bronchus and trachea, while the larger middle tracheobronchial node lies in the angle formed by the origin of the primary bronchi. Occasionally, there is a fourth node that lies just cranial to the right node and rarely, pulmonary nodes are present on one side beyond the left or right tracheobronchial node, on the dorsal surface of the primary bronchi (Evans and Christensen 1979).

The thymus gland is located in the cranial mediastinum, and reaches a maximum size at four to five months of age, when it extends from the thoracic inlet to the heart. In the normal adult, it is atrophied, replaced by fat and is not visible radiographically (Evans and Christensen 1979, Aronsohn 1985).

There is considerable overlap between the structures drained by the mediastinal lymph nodes. The sternal lymph nodes drain the diaphragm, mediastinum, pleura, thoracic wall, the cranial part of the mammary chain and the pectoral muscles. The

tracheobronchial nodes drain the lungs, bronchi, oesophagus, heart, trachea, and mediastinum. The mediastinal nodes drain both the sternal and tracheobronchial lymph nodes, as well as the cervical lymph nodes, mediastinum, oesophagus, heart, aorta and vertebrae (Hammer and Couto 1991). Thus it is logical that it if one lymphoid structure is involved, then the others are also likely to be affected by the disease process. The findings of the present study and Ackerman and Madewell (1980) confirm that enlargement of only one of the cranial mediastinal lymphoid structures is an infrequent finding in multicentric lymphoma.

Thoracic lymphadenopathy has many possible aetiologies, including infectious as well as neoplastic conditions (Couto 1989, Hammer and Couto 1991). Bacterial pathogens associated with lymphadenopathy include *Actinomycetes*, *Nocardia* and *Mycobacterium* (tuberculosis), which may cause regional enlargement of the thoracic nodes. Others such as *Brucella*, *Borrelia*, and agents involved in bacterial endocarditis, are associated with a generalised lymphadenopathy. Fungal diseases such as histoplasmosis, blastomycosis and coccidiomycosis also cause thoracic lymphadenopathy, but are extremely rare in the UK, except in recently imported dogs. Rickettsial and parasitic disease may cause generalised lymphadenopathy with involvement of the thoracic nodes (Urquhart and others 1987): leishmaniasis due to *Leishmania donovani infantum* has been seen in three patients in our hospital within the last 3 years, all of which had been born in Spain and imported to the UK as young animals. Although leishmaniasis is unlikely to become endemic in the UK it may increase in frequency as the movement of people and animals between this country and continental Europe increases (Guy and others 1993).

Many neoplastic lesions may infiltrate the thoracic nodes: these include mammary carcinomas, melanomas, pulmonary carcinomas, fibrosarcoma, and osteosarcoma. Thoracic lymphadenopathy is also seen in malignant histiocytosis (Shaiken and others 1991), which is a systemic malignancy characterised by proliferation of anaplastic reticuloendothelial cells that invade multiple organs. Primary mast cell tumours have been reported to arise from the tracheobronchial nodes, but this is extremely uncommon (Macy 1985).

Occasionally, non-infectious non-neoplastic conditions can cause enlargement of the thoracic lymph nodes. For example, auto-immune conditions including systemic lupus erythematosus, rheumatoid arthritis and other polyarthritides can cause thoracic node enlargement as part of a generalised lymphadenopathy. Thoracic lymphadenopathy must be marked before it is detectable radiographically, and these conditions generally do not cause lymphadenopathy of such proportions. Lymphadenopathy which is radiographically detectable is seen most commonly in

association with lymphoma, malignant histiocytosis, mycobacterial infections, and other granulomatous infections, and occasionally as a result of metastatic disease or leukaemia. Although Myer (1980) concluded that tracheobronchial lymphadenopathy is usually more prominent in animals with granulomatous pneumonia than in animals with pulmonary metastases from a non-systemic tumour, Mitten (1982) recorded secondary involvement of the tracheobronchial nodes which caused profound enlargement.

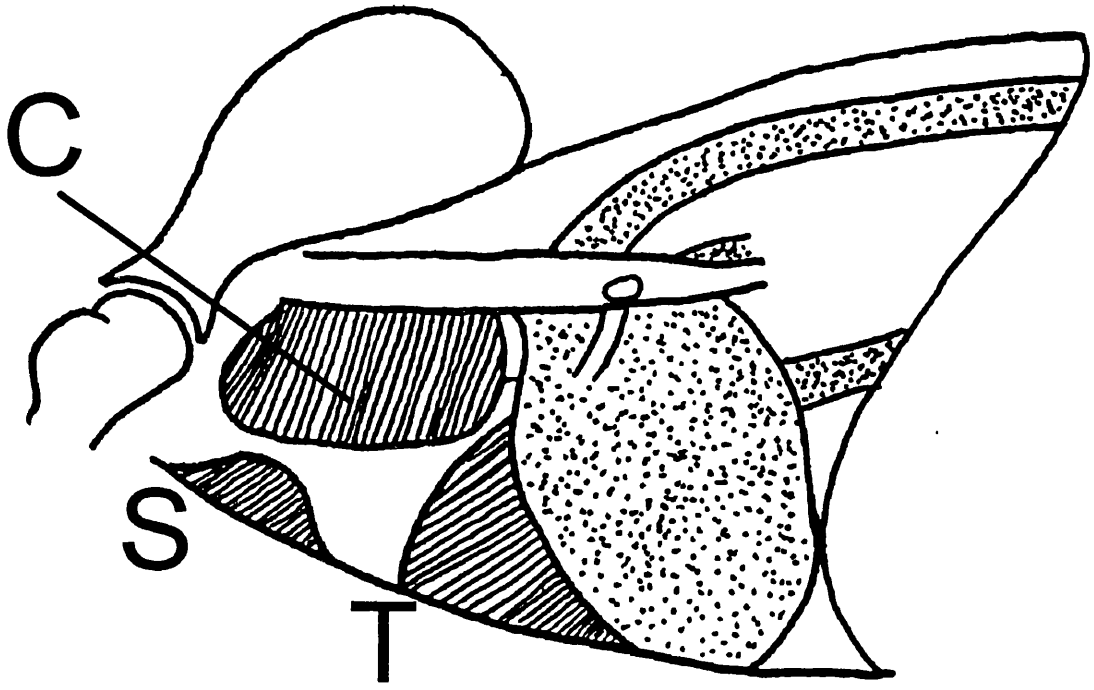
Cranioventral mediastinal masses which must be differentiated from suprasternal or cranial mediastinal lymphadenopathy or thymic enlargement include mediastinal abscesses and granulomas, lipomas, thymomas, ectopic thyroid and parathyroid tumours and localised haematomas (Mitten 1982, Suter and Lord 1984a). In addition, cranial lung masses, especially in the right cranial lobe, may mimic cranial mediastinal masses on the lateral view (Mitten 1982). Mediastinal abscesses and granulomas often result from mediastinitis or the migration of foreign bodies into the mediastinum from the neck, oesophagus or trachea (Suter and Lord 1984a). Fungal granulomas are rare in the UK but may be accompanied by thoracic lymphadenopathy and pulmonary change making differentiation from lymphoma impossible radiographically (Suter and others 1974). Loculated fluid accumulations within the mediastinum can also be confused with lymphadenopathy or thymic enlargement (Suter and Lord 1984a). Mediastinal widening on the dorsoventral view due to fat accumulation may be generalised or localised, making differentiation from lymphadenopathy or thymic enlargement more difficult (see below).

Table 3.5 compares the incidence of mediastinal disease found by Ackerman and Madewell (1980) and this study.

	Ackerman and Madewell (1980)	**Blackwood (1993)**
Radiological Abnormality	Number affected (%)	Number affected (%)
Suprasternal lymphadenopathy	60 (60%)	34 (40%)
Tracheobronchial lymphadenopathy	47 (47%)	28 (33%)
Cranial mediastinal change	36 (36%)	22 (26%)
Thymic infiltration	Not reported.	6 (7%)
Total number of cases	100	84

Table 3.5: Mediastinal disease in lymphoma patients.

The radiographic locations of cranial mediastinal lymphadenopathy and thymic enlargement on the lateral thoracic radiograph are shown in diagrammatic form (Figure 3.10). This diagram illustrates where changes are most likely to be seen, and does not reproduce the actual appearance of cranial mediastinal lymphadenopathy or thymic enlargement. In addition, enlarged structures may extend beyond the limits of the areas designated.



(S-suprasternal nodes, C-cranial mediastinal nodes, T-thymus).

Figure 3.10: Diagrammatic representation of the locations of cranial mediastinal abnormalities associated with lymphoma.

Sternal lymphadenopathy

Enlargement of the sternal lymph nodes is one of the most common signs of lymphoma in dogs (Ackerman and Madewell 1980, Suter and Lord 1984a). The enlarged suprasternal nodes appear as a soft tissue mass dorsal to the second and third sternebrae. These masses have a convex dorsal margin, and this distinct margin can be helpful in differentiating them from fat in this region (Burk and Ackerman 1986b).

Ackerman and Madewell (1980) found sternal node enlargement in 60% of the 100 cases they reviewed, and this change was the commonest thoracic abnormality recorded. Although the results of the current study reflect a lower frequency of detection this finding was again the most common thoracic radiological abnormality, affecting 40% of the 84 animals in the study group. Kene (1984) recorded a soft tissue mass dorsal to the cranial sternebrae (which we must assume corresponds to the suprasternal node) in 9 of 22 (41%) cases reviewed, and once again this was the most commonly enlarged thoracic node. Sternal lymphadenopathy can occur in other diseases, but the frequency of occurrence in such situations is unknown. The present study found sternal node enlargement to be the only thoracic radiographic abnormality in seven (8%) of the cases; similarly, Ackerman and Madewell (1980) found this solitary lesion in only 10 of 100 (10%) patients. However, in both studies, enlargement of this node without radiographically detectable enlargement of either the cranial mediastinal or tracheobronchial nodes was seen more frequently than isolated enlargement of either of the other nodes. These findings are in also agreement with those of Suter and Lord (1984a), who reported that enlargement of this node is one of the earliest and most common radiographic features of lymphoma. It may be that in those cases where suprasternal lymphadenopathy was the only radiographically detected thoracic abnormality, further changes would have become visible as the disease progressed.

The main problem encountered in detection of suprasternal lymphadenopathy was poor positioning as a result of inadequate forward distraction of the fore limbs. This problem was encountered in 28 (33%) of cases in this survey group, but in these animals it was decided that careful examination allowed assessment of the sternal node. However, it is possible that this contributed to the lower incidence of sternal lymphadenopathy recorded in this study compared to that of Ackerman and Madewell (1980) as viewers may have been cautious of over interpreting density in the suprasternal position if this was in any way obscured. Indeed, a number of cases in which the positioning was so poor that no assessment of the suprasternal nodes could be made had been excluded from the study group during initial selection. The frequent occurrence of imperfect positioning may reflect a reluctance to sedate adequately animals which were often systemically ill. Ackerman and Madewell (1980) and Kene (1984) made no comment on such positioning problems. Burk and Ackerman (1986b), indicated that if the fore limbs were not pulled cranially, their density could produce either artefactual densities in the suprasternal and cranial mediastinal areas or obscure existing mediastinal or

pulmonary lesions. Adequate positioning is a prerequisite for accurate radiographic assessment of lymphoma patients.

Ackerman and Madewell (1980) reported that in three of the 100 cases it was impossible to comment on the sternal lymph node because of pleural fluid or confluence with other nodes. No such nodal confluence was noted by Kene in 1984, though it is unclear whether some of the suprasternal lymph nodes merged with the cranial mediastinal nodes. In the current study, there were no cases where the suprasternal node merged with the cranial mediastinal nodes, but there was one case where the cranial border of the enlarged thymus merged with the cranial mediastinal nodes, but it appeared that there were two separate structures which were in contact rather than one indefinable cranial mediastinal mass. In six of the seven dogs with pleural fluid the suprasternal nodes were obscured to some extent, and in all six of these cases the cranial mediastinal nodes were obscured either completely or partially by the fluid. Where a very small amount of fluid was present, this tended not to obscure the nodes. Kene (1984) made no mention of obscuring of the cranial mediastinal nodes by free pleural fluid, despite mentioning that the cardiac shadow was completely obscured by fluid in one of the two cases with effusion: it is extremely unlikely that the nodes were visible in this case. It must be assumed that in those cases reviewed by Ackerman and Madewell which had concurrent suprasternal or cranial mediastinal lymphadenopathy and pleural effusion that the volumes of fluid were small.

Cranial mediastinal lymphadenopathy and thymic enlargement

In this study, dorsoventral radiographs of good quality were available for only a minority of the patients. The diagnosis of cranial mediastinal lymphadenopathy was thus based on the presence of soft tissue density or densities within this region ventral to the trachea on the lateral view, which were distinct from the sternal nodes and did not occupy the position of the thymus (Figure 3.10, page 35). In some cases, the trachea was deviated either dorsally or laterally by these densities. This was an inconsistent finding. It is recognised that the position of the patients neck affects the tracheal position: flexion of the neck into the chest can produce dorsal bowing of the trachea on the lateral view, or a right lateral displacement of the trachea on the ventrodorsal or dorsoventral view. Bowing of the trachea to the right is seen commonly in both chondrodystrophoid breeds and brachycephalic breeds (Myer 1978b, Mitten 1982). Myer (1978b) states that only those instances of tracheal deviation associated with a soft tissue mass should be considered significant. Kene (1984) reports that the soft tissue masses seen in the cranial thorax of 13 of a series of 22 dogs with lymphoma deviated the trachea in only three cases. However, very large cranial mediastinal masses may compress the tracheal

lumen or displace the tracheal bifurcation and cardiac shadow caudally. This was not seen in any of the cases reviewed in the current study.

The cranial mediastinum of the normal dog should be of similar width to the vertebral column on ventrodorsal or dorsoventral radiographs. Widening of the cranial mediastinum may result from the accumulation of fat within it (Mitten 1982, Suter and Lord 1984a, Burk and Ackerman 1986a, Myer 1978b). The radiographic difference in density between fat and soft tissue can be difficult to appreciate in this area, due to the superimposition of other structures in the dorsoventral view, where the width of the mediastinum is assessed. Additionally, fat may accumulate in the mediastinum in a generalised or localised distribution: in the latter situation it can be more difficult to differentiate fat from a mass lesion. However, mediastinal widening due to fat has a very smooth margin and the trachea of such fat animals is not deviated, tending to sit in its normal position (Myer 1978b). An apparent widening of the mediastinum can also be seen in sternal recumbency in cases with pleural effusion where fluid accumulates along the sternum (Myer 1978a, Mitten 1982). In this situation other changes such as blunting of the costophrenic angles, outlining and flaring of interlobar fissures and obscuring of the cardiac apex by a fluid or soft tissue density should alert the radiologist to the presence of pleural effusion.

Enlargement of the cranial mediastinal lymph nodes was seen in 22 (26%) of the cases in this series. Cranial mediastinal widening was identified in 36 of the 100 (36%) cases reviewed by Ackerman and Madewell in 1980. It can be assumed that enlargement of the cranial mediastinal nodes was the cause of the mediastinal widening in the majority of the affected cases in the study carried out by Ackerman and Madewell (1980), as this change is much commoner than thymic enlargement. Suprasternal lymphadenopathy was evaluated separately from enlargement of the cranial mediastinal nodes in both studies. The slightly higher frequency of detection of abnormality may be attributed to a number of possible causes including greater radiographic sensitivity to this change in the previous study, where dorsoventral radiographs of the thorax were available for all cases or possibly to a degree of over-interpretation of cranial mediastinal widening due to obesity or small amounts of pleural fluid. It is recognised that irregularity of the mediastinal margin is usually due to the presence of a mediastinal mass rather than fat or fluid (Mitten 1982, Burk and Ackerman 1986a), but the nature of the margin is not discussed in the paper. Greater reader sensitivity must also be considered, especially as there is a generally higher frequency of detection of thoracic node enlargement in the previous study. It is also possible that the group of patients for whom radiographs

were available in the 1980 study had more advanced and widespread thoracic disease at time of presentation.

Thymic or cranial mediastinal node density could be differentiated on the basis of the position in both lateral and dorsoventral views. Dorsoventral views were available for three of the six animals where thymic enlargement was detected: suspicion on examination of the lateral view may have prompted the additional view. The thymus was seen extending to the left of midline just cranial to the heart. It appeared as a roughly triangular soft tissue density, the apex of which was blunted by infiltration when enlarged. On the lateral views, the thymus appeared as a somewhat ill-defined soft tissue density just cranial to the heart above the sternum (Figure 3.4, page 21). Thymic enlargement was seen in only six of the 84 dogs. In one case, the cranial border of the thymic shadow merged dorsally with the caudal border of the enlarged cranial mediastinal nodes. Neither of the previous review articles (Ackerman and Madewell 1980, Kene 1984) discussed thymic enlargement as a separate entity, though a minority of the 36 patients reported by Ackerman and Madewell (1980) to have mediastinal widening may have had thymic enlargement. Mitten (1982) stated that the recognition of individual soft tissue densities within the cranial mediastinum can be difficult, and this may be the reason Ackerman and Madewell (1980) chose to record their findings in this way. However, the results of the current study would suggest that these structures can generally be identified individually. As thymic or cranial mediastinal node enlargement becomes very marked, the structures may become radiographically confluent.

In the dog, lymphoma is the most common neoplasm to affect the mediastinal structures. Thymic enlargement due to the presence of a thymoma (a neoplasm of the thymic epithelial cells) is rare (Couto 1989). Local metastatic extension to surrounding structures and metastases to lungs, liver, spleen, lymph nodes and diaphragm have been reported in a some cases of thymoma (Aronsohn 1985) but many thymomas do not extend beyond the thymic remnant. Thymomas and lymphoid infiltration of the thymus cannot be differentiated radiographically. The author has found that cytological evaluation of samples obtained by fine needle aspiration from thymic lesions due to lymphoid neoplasia is generally diagnostic. In contrast, Aronsohn (1985) reports inconsistent results when using this technique to diagnose either thymomas or lymphoma. However, given the frequency of occurrence of lymphoma compared to primary thymic neoplasia, this disease must be ruled out in cases of thymic enlargement, and aspiration cytology may rapidly allow a diagnosis to be made.

Tracheobronchial lymphadenopathy

The middle tracheobronchial lymph node lies dorsocaudal to the carina on the lateral radiograph. The right and left tracheobronchial nodes are seen just cranial to the carina, where the right tends to lie ventral to the trachea and the left dorsal to the trachea (Mitten 1982, Suter and Lord 1984a). In this study the lateral thoracic radiograph was most useful for detection of tracheobronchial lymphadenopathy, which was often less clearly defined on the dorsoventral view due to the anatomical complexity of this area and superimposition on the cardiac shadow.

The differential diagnoses for hilar and perihilar masses includes lymph node enlargement, oesophageal foreign bodies, chemodectomas, and other miscellaneous masses such as ectopic thyroid tissue and haemangiosarcoma. Additionally, cardiac and vascular abnormalities, where the aorta, pulmonary artery or left atrium may masquerade as masses, must be differentiated from the tracheobronchial nodes (Mitten 1982, Suter and Lord 1984a). Oesophageal foreign bodies associated with mediastinal inflammation often have a hazily marginated appearance and can thus appear similar to tracheobronchial lymphadenopathy should they become lodged at the level of the hilus. The other lesions tend to have more distinct margins, but the concurrent presence of pulmonary oedema in cases where vascular abnormality is associated with left heart failure could lead to blurring of the margins, as in the case of an enlarged left atrium. However, in such a case the left atrium will tend to push up between the mainstem bronchi and elevate the left mainstem bronchus more than the right, whereas an enlarged tracheobronchial node impinges on the bronchi from a more dorsal position. Other radiographic evidence of the primary cardiac problem such as chamber enlargement, pulmonary vascular changes or hepatomegaly would aid differentiation.

Hilar soft tissue masses are most often due to tracheobronchial lymphadenopathy (Suter and Lord 1984a). These lymph nodes may be enlarged secondary to pulmonary or pleural infection or neoplasia, as well as many systemic diseases (see above). Lymphadenopathy due to tuberculosis, nocardial pleuritis, actinomycosis, and fungal infections is often large enough to be seen radiographically as a hilar mass, but lymphadenopathy caused by most other bacterial or viral thoracic infections is generally of insufficient size to allow appreciation of the enlarged tracheobronchial nodes as a hilar mass on radiographs (Suter and Lord 1984a). Infrequently, lymphadenopathy associated with primary or metastatic lung tumours is reported to be detectable radiographically, but secondary involvement of the nodes can result in profound enlargement of the tracheobronchial lymph nodes (Mitten 1982) Tracheobronchial lymphadenopathy large enough to be detected

radiographically has been reported in association with lymphoma, mast cell tumours, and the much rarer conditions malignant histiocytosis (Wellman and others 1985, Shaiken and others 1991) and lymphomatoid granulomatosis (Postorino and others 1989b). Mast cell tumours arising from the tracheobronchial lymph nodes are extremely rare (Macy 1985).

The detection of tracheobronchial lymphadenopathy was subject to much inter-viewer disagreement on initial examination. Both false positives and negatives were recorded, suggesting that this presented a genuine problem in interpretation rather than merely being a change that was easily overlooked. Myer (1978b) stated that tracheobronchial lymphadenopathy can cause ventral displacement of the mainstem bronchi or carina. Additionally, displacement or compression of the trachea or primary bronchi as a result of tracheobronchial lymphadenopathy is reported by Mitten (1982) and Suter and Lord (1984a). Mitten (1982) stated that the deviation of the trachea or bronchi created by enlarged tracheobronchial nodes may be dramatic, and that in severe cases occlusion of the compressed mainstem bronchus may occur. Deviation or compression of these structures may be the only clear radiographic change seen because the lymph node borders are often obscured by concurrent increase in pulmonary density (Burk and Ackerman 1986a).

In the current study, there were no cases where the enlargement of the tracheobronchial lymph nodes, even if marked, caused a dramatic compression of the trachea or bronchi, nor to occluded a bronchus. Also, tracheobronchial lymph node enlargement was never detected on the basis of tracheal or bronchial displacement or compression alone: there was always a concurrent increase in soft tissue density in the perihilar region.

In our experience, tracheobronchial node enlargement is difficult to define and often appears radiographically as a rather ill-defined hazy increase in opacity in the hilar region. Suter and others (1974) similarly described the ill-defined hilar opacities representing the enlarged lymph nodes in cases of lymphoma. In the present study, the appearance of the perihilar area was subject to some variation. In some cases, the nodes caused dorsal deviation of the trachea immediately cranial to the bifurcation, as a result of enlargement of the right tracheobronchial node, which tends to lie ventral to the trachea on the lateral thoracic view. Ventral deviation of the trachea at the bifurcation due to enlargement of the middle and/or the left tracheobronchial node was also seen. Less commonly, deviation of a primary bronchus was detected, either ventrally due to enlargement of the middle tracheobronchial node or caudally due to the enlargement of the right tracheobronchial node (Figure 3.2, page 19). Where there was any compression of

these structures (apparent as a reduction in the diameter of the air filled lumen) this was not marked, in contrast to the findings of Mitten (1982), who reported that enlargement of the tracheobronchial lymph nodes in either inflammatory or neoplastic disease tended to impinge severely on the mainstem bronchi and trachea.

Ackerman and Madewell (1980) saw tracheobronchial lymphadenopathy in 47 of the 100 (47%) cases reviewed, compared to 28 of the 84 (33%) cases reviewed in the current study. This higher incidence may again be due to greater sensitivity due to the availability of dorsoventral radiographs for all cases (though the current study suggests that the lateral view is of more value in the detection of tracheobronchial lymphadenopathy), greater reader sensitivity or the examination of a population with more advanced disease. However, Kene (1984) saw a perihilar soft tissue at the level of the tracheal bifurcation in only two of the 22 (9%) cases he reviewed, and it must be assumed these densities represented the enlarged tracheobronchial lymph nodes. This variation in frequency of detection may reflect the difficulty in detection of this change.

Tracheobronchial lymphadenopathy is a valuable clue to the radiographic diagnosis of lymphoma, as this node is obscured less commonly by pleural fluid than the suprasternal or cranial mediastinal nodes. It is the most commonly seen enlarged node in animals with pulmonary infiltrate, and this finding increases the specificity of the pulmonary findings greatly. Ackerman and Madewell (1980) found, in a retrospective survey of 100 cases, that 21 of the 33 animals which had abnormal pulmonary density had concurrent tracheobronchial lymphadenopathy. In the current study, 14 of the 31 animals with pulmonary infiltrates had concurrent tracheobronchial lymphadenopathy. However, similar pulmonary changes accompanied by lymphadenopathy may be seen in malignant histiocytosis (Shaiken and others 1991) or mycotic infection (Suter and others 1974, MacEwen and Young 1989). These diseases are very much more uncommon than lymphoma in the UK. Thus the presence of tracheobronchial lymphadenopathy assists in alerting the radiologist to the possibility of lymphoma in animals with abnormal pulmonary density.

PULMONARY CHANGE

Identification of interstitial pulmonary disease

Thoracic radiography is rather insensitive to early pulmonary malignancies, mainly because to be visible radiologically a mass lesion may have gone through 27 to 30

tumour cell doublings (Lang and others 1986). The absolute lower limit of miliary nodule diameter for radiographic detection of a solitary soft tissue mass or a small number of lesions ranges from 3-10mm, and is influenced by the site of the lesion (Suter and others 1974, Thrall 1979, Myer 1980, Suter and Lord 1984a). However, smaller nodules may be detected due to superimposition either on each other or the cardiac shadow, ribs and diaphragm. The diffuse nature of the patterns seen in lymphoma enhance the radiographic sensitivity by simple summation of a large number of microscopic interstitial structures. However, the recognition of small nodules requires optimal lung inflation (Suter and Lord 1974, Thrall 1979).

The interstitium surrounds and supports the blood vessels, lymph vessels, alveoli and bronchi. The normal interstitial structures are not visible on conventional radiographs (Suter and Lord 1974). Diseases of the vessels, alveoli and bronchi may result in characteristic radiographic appearances which are thus not classified as interstitial disease, having their own unique patterns. However, interstitial infiltration is involved in almost all pulmonary conditions and may be the most recognisable pattern seen in a variety of pathological processes (Myer 1980). It is the most difficult of all patterns to identify, describe and interpret. Extensive interstitial disease may not be diagnosed radiographically, or an interstitial pattern may be seen radiographically in the absence of corresponding clinical signs. Interstitial patterns are generally described as disseminated or localised, then further defined as unstructured, nodular (miliary if the nodules are small) or linear (reticular) (Suter and Lord 1974). Combined reticulonodular densities are also seen.

Unstructured interstitial markings manifest as a diffuse increase in pulmonary density which obscures the smaller pulmonary vasculature and gives an overall increase in density with haziness: the increase in the ratio of interstitial tissue to alveolar air spaces diminishes the contrast within the lung field. Occasionally, small, barely visible nodular or reticular markings may be seen within the parenchyma. This type of pattern is seen in interstitial oedema, hypostasis (due to recumbency), interstitial pneumonia (for example of viral origin, and in the early and healing phases of other pneumonias), interstitial haemorrhage (due to trauma, coagulopathies), in the early and late stages of fungal disease, in early dirofilariasis and as result of pulmonary fibrosis in older dogs.

The reticular pattern refers to multiple short indistinct non-vascular curvilinear markings and the reticulonodular to a combination of both these short linear densities and small miliary nodules (Myer 1980). Miliary nodules are nodules of 2-5mm in diameter and may be poorly demarcated or have irregular margins. It is

recognised that miliary nodulation is compatible with haemic spread of disease. The pattern of smaller irregular rather indistinct opacities is very non-specific and is commonly seen in old dogs (Suter and Lord 1974). Miliary nodulation can also be associated with granulomatous diseases, dirofilariasis, metastases, and primary disseminated lung tumours (especially bronchiolar-alveolar carcinoma). Larger, clearly demarcated rounded nodules of 3mm or more are the last form of interstitial disease, and are the classical finding in metastatic neoplasia (Suter and others 1974).

True "honeycombing" as described in man is identified rarely in the dog. This manifests as radiolucent areas surrounded by strands of interstitial tissue, and is seen usually in association with bronchiectasis or focal pulmonary fibrosis as a sequela to chronic pulmonary disease. This type of change is not generally associated with lymphoma, but the term "honeycombing" is rather non-specific and has been used by some authors to describe the reticular pattern (Reif and Rhodes 1966, Suter and others 1974).

Differential diagnoses of pulmonary patterns seen in lymphoma patients

Prior to the retrospective study undertaken by Ackerman and Madewell in 1980, it had been recognised that lymphoma may produce a disseminated interstitial infiltrate of reticulonodular, micronodular or reticular type (Reif and Rhodes 1970, Suter and Lord 1974, Suter and others 1974). Suter and others (1974) described the pattern seen in most cases of lymphoma as a reticulonodular pattern composed of small irregular opacities. Pulmonary infiltration with lymphoma was associated rarely with other types of pattern such as alveolar or bronchial infiltration. It was also recognised that in some cases linear densities are seen which do not represent interlobar fissures highlighted by pleural thickening or effusion, but dilated lymphatic vessels (Suter and others 1974). Such densities are also one of the components of the interstitial pattern seen commonly, but may occasionally manifest as a rather striking radiopaque linear density which is more distinct and longer than the short linear markings seen in the reticular pattern.

The subtle radiographic patterns of generalised interstitial disease are easily masked or mimicked by a number of factors. Underexposure, underinflation and movement blur can produce densities which mimic diffuse interstitial change. Also, interstitial markings may reflect previous rather than current disease (Myer 1980, Suter and Lord 1974), or the chronic effects of microbiological or chemical irritants such as air pollutants (Reif and Rhodes 1966, and 1970).

Non-neoplastic causes of a disseminated interstitial pattern of the types seen in cases of lymphoma include interstitial oedema, pneumonia and haemorrhage (which usually give an unstructured appearance), dirofilariasis (which may produce a micronodular pattern in the early stages of the disease) and, importantly in lymphoma patients, senescent change. In addition, fungal infection (especially histoplasmosis and blastomycosis) produces pulmonary change similar to that seen in lymphoma with associated thoracic lymphadenopathy (Suter and Lord 1974, MacEwen and Young 1989). Cardiogenic oedema in left sided heart failure may appear as an increase in interstitial markings before perihilar alveolar densities develop, for which lymphoma is a differential (Biery 1974). Pulmonary contusions may result in a diffuse interstitial or mixed interstitial-alveolar pattern (Myer 1979). Pulmonary infiltration with eosinophilia can appear occasionally as disseminated ill-defined interstitial nodules or a diffuse alveolar-interstitial pattern: these patterns may partially obscure the thickened peribronchial shadows (Figure 3.11, page 50). Thus this disease may be a differential for the pulmonary changes seen with lymphoma (Cantwell 1987) Atypical cases of bronchopneumonia may occasionally mimic the findings in lymphoma, and chronic bronchitic change is also a differential (Dennis 1991).

Neoplasms which result in this type of diffuse interstitial pulmonary pattern must reach the lungs via the vascular or lymphatic system. Disseminated interstitial infiltrates secondary to neoplasia usually produce either a reticular pattern or a mixed reticular and miliary nodular pattern evenly distributed throughout the lungs (Myer 1980). This is most commonly associated with lymphoma. Burk and Ackerman (1986a) state that this change may be more marked in the hilar and perihilar area, but this prominence may reflect the anatomic complexity of the area and enhancement due to superimposition and summation, especially where there is concurrent tracheobronchial lymphadenopathy, rather than preferential involvement of the perihilar pulmonary tissue. Systemic mast cell tumours very rarely involve the lung, but if this occurs the pattern seen, if radiographically detectable, is a diffuse interstitial infiltrate (O'Keefe 1990). Cutaneous mast cell tumours do not in general spread to the pulmonary parenchyma unless systemic mastocytosis occurs (Davies and others 1981).

Adams and Dubeilzig (1978) reported diffuse pulmonary alveolar septal metastases from scirrhous mammary carcinomas in four dogs. In one of the four cases reported by these authors, there was disseminated interstitial infiltration and radiographically detectable suprasternal lymphadenopathy, while another developed a mixed-alveolar interstitial pattern. Kingston (1986) reported disseminated alveolar-interstitial patterns in cases of primary pulmonary adenocarcinomata. A

mixed alveolar-interstitial pattern was seen in two of the cases of lymphoma with pulmonary infiltration in the present study. Tiemessen (1989) reported two cases of metastatic mammary gland tumours which appeared as diffuse ill-defined interstitial nodules, for which lymphoma was included as a differential diagnosis. The author has also seen a diffuse micronodular interstitial pattern in an atypical case of metastatic prostatic adenocarcinoma. Malignant histiocytosis is frequently associated with pulmonary infiltration, which may manifest as a diffuse mixed interstitial and alveolar pattern, or occasionally as a mass lesion (Shaiken and others 1991). As malignant histiocytosis is also associated with thoracic lymphadenopathy, this relatively rare neoplasm must be included as a differential to lymphoma, especially in predisposed breeds. This condition is primarily associated with Bernese Mountain Dogs, but is seen more frequently in Rottweillers and Retrievers than in other breeds (Shaiken and others 1991). Lymphomatoid granulomatosis has been reported to cause a diffuse interstitial infiltrate, but this is usually accompanied by large pulmonary mass lesions or severe lobar consolidation as well as tracheobronchial lymphadenopathy (Postorino and others 1989b). This condition is also very uncommon.

Senescent/environmental pulmonary change

Changes which are commonly seen in the lungs of older dogs without clinical evidence of current pulmonary or cardiovascular disease include an increase in curvilinear non-vascular interstitial markings, the presence of small rather ill-defined nodules within the parenchyma, pleural and pulmonary osteomas and increased density or prominence of the tracheal and bronchial walls (Reif and Rhodes 1966). These changes may be seen in varying degrees, from barely detectable to advanced (Reif and Rhodes 1966, 1970). The more advanced cases are interpreted as evidence of chronic, non-specific pulmonary disease and may show clinical disease. In other cases, the change is less severe and is defined as senescent change. Pulmonary change also occurs in dogs as consequence of living in an urban environment, where it is thought that chronic exposure to irritants of a microbiological or chemical nature can lead to interstitial fibrosis in older dogs (Reif and Rhodes 1966, 1970) Most of the study group were urban dogs. Thus age-related and environmentally induced change may mimic both the reticular and miliary appearance seen in lymphoma.

Bronchial calcification, and increases in density of the tracheal and bronchial walls are a common finding in older dogs (Suter and Lord 1974, Reif and Rhodes 1966). Thin peribronchial shadows were seen in many of the patients in the study group and were dismissed as innocuous senescent change.

Comparison of pulmonary patterns identified in lymphoma

Reif and Rhodes (1970) reported 100% sensitivity for the radiographic diagnosis of lymphoma, described as hilar and parenchymal. This high degree of sensitivity must be interpreted with caution. In their study, true positives included all those instances in which the radiographic interpretation was consistent with the histopathological diagnosis, though not necessarily specific for it. Thus the 100% sensitivity merely reflects that patterns of change compatible with lymphoma were identified in all the lymphoma cases, not that a radiological diagnosis of lymphoma was made. Also, the description of the disease as hilar and parenchymal suggests that all of the cases examined had concurrent tracheobronchial lymphadenopathy. Only seven animals with lymphoma were included in the study group of 336 dogs.

Suter and others (1974) reviewed the thoracic radiographs of 159 dogs and cats with primary or metastatic lung tumours. This included only eight cases of lymphoma. In seven of these cases, a disseminated interstitial reticulonodular pattern was seen. This was described as consisting of a widely disseminated, rather indistinct nodules of 3-5 mm in diameter with short indistinct linear densities representing engorged lymphatics, and a varying degree of reticulation (described by these authors as "honeycombing"). All eight of these dogs had concurrent enlargement of hilar or cranial mediastinal lymph nodes, which increased the specificity of the radiological findings. This type of change is typical of lymphoma, but in the absence of lymphadenopathy can only be suggestive of a diagnosis. In the remaining case a solitary pulmonary nodule was seen.

Ackerman and Madewell (1980) reported that 33 (33%) of 100 cases of multicentric lymphoma showed an "abnormal pulmonary density". This change was defined as increased interstitial or alveolar densities. The 33 cases break down into 29 cases where diffuse interstitial density was seen, one case where well-defined rounded masses were identified, one dog where a focal alveolar density was seen, one dog where there was a focal increase in interstitial markings and one dog about which no further comment is made. Diffuse interstitial markings (of micronodular or reticulonodular type) were the most common finding in the present study. However, a proportion of the dogs showed a prominent peribronchial infiltrate, and it is possible that lymphoid infiltration was responsible for this appearance in some of these patients. Dennis (1991) recorded chronic bronchitic change as a differential for the disseminated change seen in lymphoma. Given the age of the patients, chronic bronchitic change is an important differential for these thickened shadows. Alveolar infiltration was an infrequent finding in both study groups, and was accompanied by ill-defined nodular change when seen in the current study.

However, MacEwen and others (1981) identified a mixed pattern of diffuse interstitial and alveolar densities in 16 of 51 (29%) animals involved in a cyclic combination chemotherapy trial, and commented that regression of the pattern on instigation of chemotherapy was of no value in evaluating chemotherapeutic response. No comment was made on the presence of other thoracic radiological abnormalities in this paper.

Kene (1984) reviewed the thoracic radiographs of 22 dogs with lymphoma (in any form) and found that five of these had a reticular pattern and six a diffuse pulmonary infiltrate. Unfortunately, no further comment was made on the nature of this diffuse infiltrate. This author also reported the occurrence of a "radiopaque linear density" in nine cases. This linear density is distinct from interlobar fissure thickening, which is reported separately and is most likely another description of the non-vascular curvilinear markings seen in interstitial infiltration, and/or dilated lymphatics. No comment is made on the concurrent presence of thoracic lymphadenopathy.

In seven of the 31 cases (of 84) which had radiographic evidence of pulmonary infiltration in the present study, this was the only recognised thoracic abnormality. Similarly, Ackerman and Madewell (1980) found that only four of the 33 affected animals in their study group showed abnormal pulmonary density as the sole thoracic abnormality. It is more common to find evidence of pulmonary infiltration accompanied by thoracic lymphadenopathy, and this greatly enhances the specificity of the findings (Suter and others 1974, Myer 1980). Twenty one of the 31 dogs in the current study group had evidence of thoracic lymphadenopathy as well as pulmonary infiltration.

It must be considered that the pulmonary changes seen in animals with no other thoracic radiological evidence of the primary disease may in some cases reflect senescent pulmonary change, change secondary to previous or intercurrent pulmonary disease of another aetiology, or artefactual increases in density due to technical factors. It is also possible that the viewers in both studies tended to diagnose the presence of change more frequently because they knew the patients had lymphoma: expectation of positive findings has been proven to increase the frequency of identification of radiographic abnormalities (Garland 1949). Thus it is possible that the prior knowledge of the presence of disease prejudiced the interpreter when he or she was unsure. Valli (1993) stated that histopathologically involvement of the lung in lymphoma is rare, which is in direct contradiction to the radiological findings of the current study and the studies undertaken by Ackerman and Madewell(1980), MacEwen and others (1981) and Kene (1984).

Unfortunately, these radiological observations are not substantiated by pathological findings.

A solitary lesion was seen within the pulmonary parenchyma of one dog within the study group (Figure 3.8, page 27). The mass remained unchanged throughout the course of the dog's treatment, and did not reduce in size when the dog went into remission. Unfortunately, the owners refused permission for post-mortem when the dog was euthanased, and no final diagnosis was made as to the nature of the mass. Given the lack of any response to chemotherapy or apparent progression on relapse of the primary disease, it is most likely that the mass was unrelated to the primary problem. The most likely diagnosis for the mass was a slow growing primary pulmonary tumour, as the solitary lesion was large, central to peripheral within the lobe and well circumscribed. These features are commonly seen in primary lung tumours in dogs (Suter and others 1974). This patient was thus not included in the pulmonary infiltrate group.

In summary, the interstitial patterns seen in lymphoma are commonly disseminated miliary nodular/micronodular or reticulonodular, and can be difficult to differentiate from senescent pulmonary change. Lymphoma may often appear result as a characteristic (but not pathognomonic) pattern which is distinctly and markedly nodular, or reticulonodular, and in the these cases is more readily differentiable from age-related pulmonary change and most other pulmonary conditions. However, where the change is subtle or has other components, it can be difficult to interpret the radiographic findings accurately. Occasionally, a disseminated alveolar-interstitial pattern may be seen. In addition, the significance of thickened peribronchial shadows in lymphoma cases is unknown. Thus lymphoma can create pulmonary patterns similar to those seen in many other conditions. The concurrent presence of hilar or cranial mediastinal lymphadenopathy is highly suggestive of lymphoma but may also be associated with either chronic fungal disease (Suter and Lord 1974), or with other neoplasms, especially malignant histiocytosis (Wellman and others 1985, Shaiken and others 1991), which may also produce the interstitial markings typically associated with lymphosarcoma.

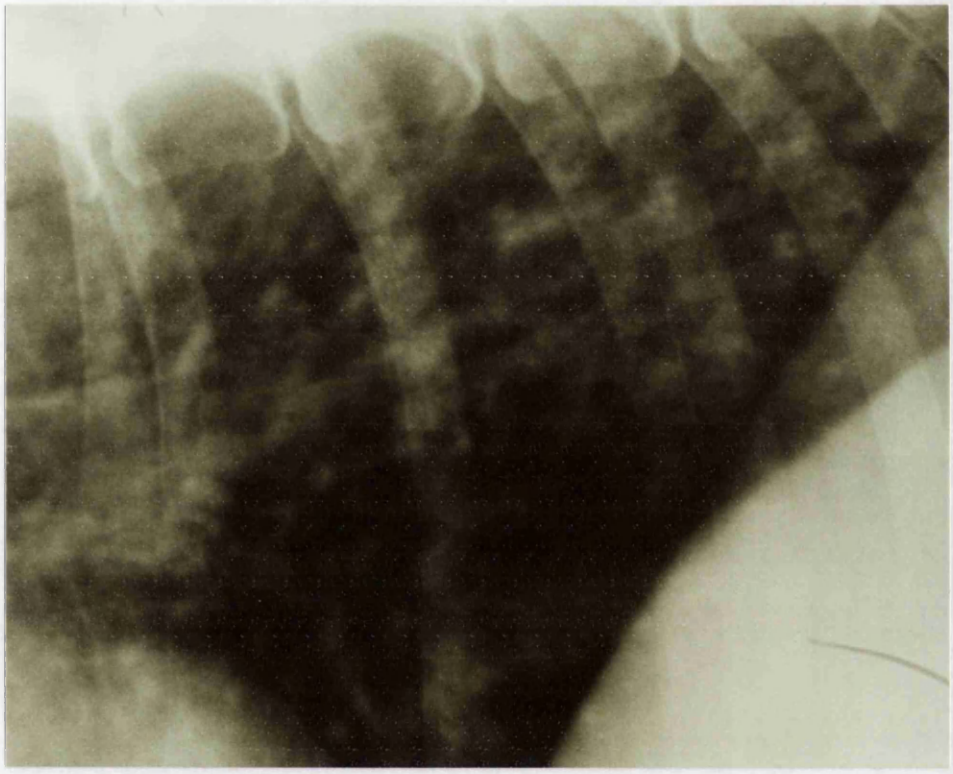


Figure 3.11: Lateral view of the thorax (close up) of a dog suffering fom pulmonary infiltration with eosinophils (P.I.E.). The pattern of change is disseminated, with coalescing diffuse alveolar-interstitial markings as well as marked peribronchial thickening. Coalescence in the perihilar region mimics tracheobronchial lymphadenopathy.

PLEURAL CHANGE

The radiographic appearance of pleural disease

The pleural space is the potential space between the visceral and parietal pleurae, and between the adjacent visceral pleura between lung lobes. It is normally occupied by a small amount of serous fluid, and as such is not visible radiographically . In obese animals, fat can accumulate below the parietal pleura and this can be seen occasionally radiographically. The width of the pleural space may also be accentuated on an expiratory radiograph in a normal animal (Burk and Ackerman 1986a).

Pleural effusion may be free or encapsulated. Free fluid is generally serous and its position is affected by gravity, and the elasticity of the diseased and normal parts of the lungs. Free pleural fluid is seen in animals with congestive heart failure, pleuritis (for example in pleuropneumonia), thoracic duct tears or ruptures, haemorrhage, diaphragmatic hernia, hypoproteinaemia and neoplasia. Encapsulated fluid is trapped within fibrinous adhesions, so cannot move under the influence of gravity (Lord and others 1972, Myer 1978a). This appearance is most commonly associated with chronic exudative effusions, such as pyothorax or chylothorax (Myer 1978a). Lord and others (1972) found that encapsulation was very uncommon, and most frequently seen after local infection from bite wounds. This appearance is not usually seen in lymphoma, unless there is neoplastic infiltration of the thoracic duct leading to chylothorax. A third category of fluid was described by Lord and others (1972)as trapped: this refers to fluid which takes up an atypical distribution but which alters its position due to gravitational forces.

Radiographically, pleural effusion results in an increase in the width and density of the pleural space. In the dog, the mediastinum is incomplete so effusions are usually bilateral. As fluid accumulates, the lung lobes collapse and retract from the chest wall. The interlobar fissures are widened and the lung edges are accentuated. Widened interlobar fissures are only visible if the x-ray beam is in a roughly parallel plane to the fissure, so that different fissures are evident on different projections.

Small amounts of pleural fluid are difficult to detect, and are most readily visible on expiration. Ventrodorsal views assist in the diagnosis of small amounts of fluid but are absolutely contraindicated in all but the lowest volume effusions due to the respiratory distress which will result from dorsal recumbency. The presence of small amounts of fluid results in blunting of the costophrenic angles on the

ventrodorsal view, and accentuation of the interlobar fissures adjacent to the spine (especially on either side of the accessory lobe). There may be apparent mediastinal widening as free fluid accumulates in the paravertebral gutters. The standing lateral position is helpful in diagnosing small amounts of fluid, and is not distressing for the patient. Additionally, the left lateral decubitus view proved very sensitive in an experimental survey undertaken by Lord and others (1972). However, both of these views require the use of horizontal beam radiography, which cannot be recommended on a routine basis.

The dorsoventral view shows apparent cranial mediastinal widening as fluid accumulates along the sternum, and widening of the interlobar fissures (initially between the accessory lobe and the diaphragmatic lobes, then also between the two parts of the left cranial lobe, and between the right cranial and middle lobes)(Lord and others 1972, Suter and Lord 1984c). On the lateral view, effusion tends to accumulate ventral to the heart and the easily collapsed cranial and middle lung lobes. Lord and others (1972) found that 100ml of fluid in the pleural space of a medium sized dog was discernible on the lateral view. As the volume increases, on the lateral view, fluid will also be seen dorsally in the costodiaphragmatic recesses as the caudal lung lobes collapse. The cardiac shadow and diaphragmatic line are obscured to a greater degree as fluid volume increases. The lungs also become increasingly collapsed, but will retain their typical shape due to form elasticity unless there is concurrent fibrinous pleuritis or pulmonary parenchymal disease. In all views, as the volume of fluid increases, retraction and separation of the lobes from the chest wall becomes apparent. Widened interlobar fissures take on a triangular appearance, and as fluid builds up the lobes collapse progressively. Occasionally, a lobe may collapse and be completely obscured by fluid: this usually affects the cranial lobes or right middle lobe (Figure 3.9, page 30). These lobes apparently offer the least resistance to compression even by relatively small amounts of fluid (Lord and others 1972).

Lord and others (1972) report that the earliest radiological sign of free pleural fluid was the accumulation of fluid along the ventral part of the thorax in the lateral recumbent position (the thin ventral edges of the lung retract easily), sometimes resulting in the appearance of dense wedges formed by the widened interlobar fissures ventrally. However, small amounts of fluid are visible inconsistently in this position due to obscuring by the overlying sternum and cardiac shadow. It is important in obese patients to differentiate fluid from fat between the heart and the sternum on the lateral view: this does not widen the interlobar fissures.

Pleural thickening manifests itself as a prominence of the interlobar fissures, most commonly the fissure between the right middle or left cranial (caudal part) and diaphragmatic lobes. This was seen as a fine non-branching linear density over the cardiac shadow on the lateral view. On the dorsoventral view, a thickened line can be seen at the lateral margins of the lung and followed medially along the interlobar fissures. It can be extremely difficult to differentiate between pleural thickening and very small amounts of pleural effusion on traditional lateral and dorsoventral views (Lord and others 1972). Pleural thickening is a non-specific reaction to a variety of diseases and may develop acutely, for example due to small volume haemorrhage in pulmonary contusion, or chronically, most commonly as a result of healed disease in older dogs (Suter and Lord 1984c).

Pleural effusion in neoplasia

Neoplasia may cause pleural effusion in several ways. Neoplastic tissue may invade the lymph nodes, or may obstruct or erode the blood vessels or the lymphatics. Invasion of the lymphatics obstructs lymph flow, so interfering with protein absorption from the pleural space. Thus the intrapleural oncotic pressure increases and the colloid osmotic pressure gradient is reduced, resulting in reduced absorption of fluid. Erosion of blood vessels and lymphatics allows haemorrhage or high protein effusion which increases intrapleural colloid osmotic pressure. Neoplasia can also lead to secondary pleuritis and atelectasis, increased capillary permeability, and hypoalbuminaemia. Where tumour tissue causes significant pleural irritation, either by its physical presence or the production of irritant substances, the thickened pleura will have a reduced absorptive capacity. Increased permeability of capillary vessels supplying tumour tissue can increase fluid formation, which may exceed the absorptive capacities of the pleura. If severe hypoalbuminaemia results from tumour effects (plasma albumin less than 15 g/dl) then pleural effusion will result directly from reduction of the colloid osmotic gradient which allows absorption (Noone 1985).

Neoplasia of the thoracic cavity is one of the most common causes of pleural effusion in the dog (Noone 1985). This author concluded that primary or secondary tumours of the thoracic lymphoid system (nodes, thymus, lymphatics) were probably the most common neoplastic cause of pleural effusion. The majority of cases presented with an anterior thoracic mass, which was usually lymphoid in origin. The volumes of fluid observed were very variable. Previously, Thrall (1983) reported that lymphoma was the most common cause of neoplastic pleural effusion in small animals. However, this author also considered feline patients, which have a high frequency of pleural effusion associated with thymic lymphoma.

In the dog, pleural effusions are also seen associated with metastatic carcinomas and adenocarcinomas, haemangiosarcomas or less commonly metastatic sarcomas or pleural mesotheliomas (Berkwitt and Berzon 1988, Orton 1985).

Senescent pleural change

Pleural thickening and resultant outlining of the interlobar fissures is seen in older animals as a result of fibrosis, calcification or both (Suter and Lord 1984c, Burk and Ackerman 1986a). Reif and Rhodes (1966) reported that pleural thickening was visible radiographically in most dogs over five years of age. 76% of the cases reviewed in this study were over five years old, and of the 12 patients with pleural thickening as the only recorded thoracic abnormality, 11 were five years old or over. Thus it is likely that pleural thickening was an inconsequential age related change in the majority of cases in which it was seen, rather than a consequence of the primary disease. It must also be considered that the detection of very small volumes of free fluid on standard views is difficult, and a minority of cases diagnosed as having pleural thickening may in fact have had very small pleural effusions accentuating the interlobar fissures.

Pleural change in lymphoma patients

Ackerman and Madewell (1980) reported that seven of the 100 cases of multicentric lymphoma reviewed had pleural effusions. Similarly, seven of the 84 animals in the current study had pleural effusion. Kene (1984) reported the presence of free pleural fluid in two of the 22 cases reviewed. Thus it appears that pleural effusion is relatively uncommon finding in multicentric lymphoma. However, the presence of a pleural effusion makes radiological diagnosis of the disease more difficult because effusion obscures the cranial mediastinal structures and leads to reduced lung inflation and collapse, making detection of subtle interstitial patterns difficult. The presence of effusion will thus greatly reduce the sensitivity to thoracic change. In four cases of the seven cases with effusion in the current study, the pulmonary pattern could not be identified as normal or abnormal due to pulmonary atelectasis. Ackerman and Madewell (1980) reported three cases in which it was impossible to comment on sternal lymph node involvement because of the presence of pleural fluid or confluence with other nodes. In the current study, the sternal node was obscured completely in four of the seven animals with pleural effusion, and obscured partially in two cases. Similarly, the cranial mediastinal nodes were masked completely in five cases and obscured partially by fluid in one case. Where nodes were obscured partially, these were massively enlarged and visible despite the presence of moderate amounts of effusion.

Kene (1984) recorded pleural thickening in 11 of the 22 cases he reviewed. Unfortunately, the age distribution of the lymphoma patients in this group is not specified, but it can be assumed that many of the patients were over 5 years of age and that the pleural thickening reported is an innocuous age-related change in the majority of these cases. In some cases, small amounts of pleural fluid may have been detected as pleural thickening. Pleural thickening was seen less commonly in the current survey, affecting only 12 of the 84 patients, but was again thought to be insignificant senescent change. The inconsequential nature of this change may be the reason why the change was not recorded by Ackerman and Madewell (1980).

It must be considered that thoracocentesis may have been performed in some cases in the current study prior to radiography, without this having been recorded. However, if this had occurred, it is likely that sufficient fluid would have remained within the thoracic cavity to allow radiographic detection. In addition, other evidence of this type of intervention such as small amounts of air within the pleural space may have alerted the radiologist to this possibility.

The erect ventrodorsal projection (horizontal beam) has been recommended by some authors to allow identification of cranial mediastinal disease where there is effusion but this view cannot be recommended as it involves unacceptable risk to personnel involved in patient restraint, in contravention to the Ionising Radiation Regulations (1985). Ultrasonographic evaluation of the cranial mediastinal structures or repeat radiography after thoracocentesis will provide the necessary information if cranial mediastinal pathology is suspected. In cases where lymphoma is suspected, in the author's experience cytological evaluation of pleural fluid will often provide the diagnosis, without these measures being necessary.

SUMMARY OF THORACIC FINDINGS

In conclusion, there are several points which can be made regarding the radiographic thoracic changes see in multicentric lymphoma. Firstly, the disease cannot be classified as a radiological diagnosis, though the findings in its most characteristic form are highly suggestive. However, a proportion of animals will show no radiographic evidence of disease. It is unusual to find a single thoracic abnormality in this disease, and the presence of thoracic lymphadenopathy should alert the radiologist to this potential diagnosis. The most common enlarged nodes detected are the suprasternal: it is imperative that care be taken in patient positioning to pull the forelimbs forward adequately to allow optimal examination of this area. In addition, tracheobronchial and/or cranial mediastinal

lymphadenopathy are commonly identified. Tracheobronchial lymphadenopathy often manifests as a rather poorly defined increase in density in the perihilar region, and this finding is subject to both over and under-diagnosis. Tracheal displacement is an unreliable indicator of tracheobronchial or cranial mediastinal lymphadenopathy, and should be interpreted with caution. Thymic enlargement is uncommon and is seen most clearly on the dorsoventral view.

Pulmonary infiltration in lymphoma is a relatively common but non-specific finding. The patterns seen commonly in lymphoma are miliary nodular/micronodular or reticulonodular, and can be difficult to differentiate from senescent pulmonary change. Lymphoma may often appear as a characteristic (but not unique) pattern which is disseminated and markedly micronodular, or reticulonodular, and in the these cases is more readily differentiable from age-related pulmonary change and most other pulmonary conditions. However, where the change is more subtle or has other components, it can be difficult to interpret the radiographic findings accurately. Occasionally, a disseminated alveolar-interstitial pattern may be seen. In addition, the significance of thickened peribronchial shadows in lymphoma cases is unknown. Thus lymphoma can create pulmonary patterns similar to those seen in many other conditions. The concurrent presence of hilar or cranial mediastinal lymphadenopathy is highly suggestive of lymphoma but may also be associated with chronic fungal disease (Suter and Lord 1974, MacEwen and Young 1989) or other neoplasms, especially malignant histiocytosis (Wellman and others 1985, Shaiken and others 1991), which may also produce the interstitial markings typically associated with lymphosarcoma. The presence of an interstitial pattern of disseminated miliary nodular or reticulonodular type should serve to remind the radiologist to examine the film for signs of lymphadenopathy, which is a frequent finding animals with patterns due to lymphoma. However, the absence of lymphadenopathy does not exclude lymphoma as a diagnosis.

Pleural effusion is recorded less frequently in lymphoma patients than lymphadenopathy or pulmonary infiltration, but is by no means rare. When effusion occurs it often obscures the cranial mediastinal structures on standard and dorsoventral views, thus making diagnosis of the underlying disease impossible. Moderate or large volumes of fluid also make it extremely difficult or impossible for the radiologist to identify abnormal pulmonary density due to reduced contrast as a result of atelectasis.

CHAPTER 4.

ABDOMINAL RADIOLOGICAL ABNORMALITIES IN DOGS WITH MULTICENTRIC LYMPHOMA

ABDOMINAL RADIOLOGICAL FINDINGS

The abdominal radiological abnormalities seen in 79 cases of multicentric lymphoma are summarised below (Table 4.1). The individual cases are listed in Appendix 1.b. (pages 111-113).

Radiological abnormalities	Number affected (%)	Size (score) 1	2	3
Hepatomegaly	42 (53%)			
Splenomegaly	36 (46%)			
Sublumbar lymphadenopathy	59 (75%)	13	29	17
Ascites / Peritoneal disease	10 (13%)			

Table 4.1: Abnormalities identified on abdominal radiographs of 79 cases of lymphoma.

In 14 of the 79 (18%) cases for which abdominal radiographs were available no abdominal abnormalities were detected. 21 (27%) patients had a single radiological abnormality. Thus 44 (55%) of the cases showed multiple abnormalities. The triad of hepatomegaly, splenomegaly and sublumbar lymph node enlargement was seen in 22 of these animals.

Lymph node enlargement

Sublumbar lymphadenopathy was the most frequently identified abdominal abnormality, and was seen in 59 of the 79 (75%) cases (Figure 4.1, page 63). These included 13 animals where the sublumbar lymph node enlargement received a score of 1, 29 cases where the score was 2 and 17 cases where the score allocated was 3. Sublumbar node enlargement was seen as the only radiographic abnormality in fifteen cases.

Mesenteric lymphadenopathy was recorded in only one of the 79 cases in the selected group.

Hepatomegaly

Hepatomegaly was seen in 42 of the 79 (53%) dogs in the sample group. The caudal hepatic margin was described as smooth and rounded in 30 cases (Figure 4.2, page 64). In seven cases, the hepatic border was irregular, uneven or undulating, while in the remaining five cases the caudal border of the liver tapered smoothly to a relatively sharp point, well beyond the costal arch.

In five of the animals recorded as having hepatomegaly, there was some loss of detail in the cranioventral abdomen. In one of these cases, the splenic outline was indistinct but the hepatic margin was clearly defined. In the remaining four of these cases, there was loss of clarity of the caudal hepatic margin. In one case, this loss of serosal detail was very subtle and affected only the hepatic border, whereas in the remaining three cases the splenic outline was also indistinct.

Twenty six of the 79 (33%) animals had concurrent hepatomegaly and splenomegaly. Of these 26, 22 also had sublumbar lymphadenopathy. Hepatomegaly as a solitary change was recorded in only five cases (approximately 6%).

Splenomegaly

Splenomegaly was seen in 36 (46%) of the 79 cases, and was never recorded as a solitary change. Splenomegaly and sublumbar lymph node enlargement without any other abdominal radiographic findings were identified in only seven cases.

In one case, the margin of the enlarged spleen was distorted, forming a rather round shadow on the right lateral projection with slight undulation of the dorsal borders. The spleen in this case was examined by ultrasound, which revealed a diffuse reduction in echogenicity. A guided fine needle aspirate was performed, which showed malignant lymphoid cells, confirming that lymphoma was the cause of the lesion.

A splenectomy had been performed on one patient six months prior to referral as treatment for a discrete splenic mass. Unfortunately, no tissue had been submitted for histopathology and the nature of this lesion was unknown.

Ascites / peritoneal disease

Ascites or peritoneal disease was seen in 10 (13%) of the cases in the study group, and was seen as a solitary change in only one animal. In most cases, there was mottling and loss of contrast in the cranioventral abdomen due to the presence of relatively small amounts of fluid or localised carcinomatosis or peritonitis. This caused a loss of clarity of the splenic margins and sometimes also of the caudal border of the liver. In one case, the splenic outline and caudal border of the liver were obscured completely, but in the remainder of the cases indistinct or blurred margins were identifiable. In two cases, the loss of contrast extended to involve the midventral as well as the cranioventral abdomen. There were no cases where a substantial amount of peritoneal fluid, obscuring all the abdominal viscera, was present. Five of the ten animals identified as having peritoneal disease had concurrent hepatomegaly, and four of these five also had splenomegaly. Sublumbar lymphadenopathy was seen in seven of the ten cases with ascites. The radiographic abnormalities detected in these patients are summarised in Table 4.2. (page 62).

Combined findings

Although all four changes were seen in only three of the 79 cases, it is clear from the results that it is unusual to find a solitary change and that most cases have two or three radiological abnormalities, the most common of which are hepatomegaly and sublumbar lymphadenopathy (33 of 79 cases), hepatosplenomegaly (26 of 79 cases) and the combination of hepatosplenomegaly and sublumbar lymphadenopathy (22 of 79 cases).

Other findings

Numerous small poorly marginated areas of increased lucency were seen affecting the lumbar vertebral bodies, transverse processes and articular facets in one lymphoma patient (Figure 4.3, page 65). In the remainder of the cases, the only bony abnormalities seen were age related degenerative changes.

Prostatomegaly was the most common incidental finding on the abdominal radiographs. This was noted in six males, all of whom were entire. One of these animals was suffering from an undiagnosed prostatic adenocarcinoma at the time of presentation. Two patients had gastric abnormalities: one of these was a metallic foreign body and the other a pyloric gravel sign.

Other incidental findings recorded on review included ventral lumbar vertebral spondylosis, evidence of degenerative change around the hip joints, mineralised disc material in the thoracolumbar disc spaces, in one case dorsal protrusion of the disc material. In the same case, there was also a marked step at the lumbosacral junction and much new bone formation at this site, which impinged into the spinal canal.

Patient	Hepatomegaly	Splenomegaly	Sublumbar lymphadenopathy (score)	Location of change	Comments on margination of liver and spleen
1	No	Yes	No	Cranioventral	Indistinct splenic margins
2	No	Yes	Yes (2)	Cranioventral	Very indistinct splenic margins
3	Yes	Yes	Yes (2)	Cranioventral	Indistinct splenic and caudal hepatic margins
4	No	No	Yes (2)	Cranioventral and midventral	Slightly indistinct splenic margins
5	Yes	Yes	Yes (2)	Cranioventral	Indistinct dorsal splenic margin
6	No	No	No	Cranioventral	Indistinct splenic and caudal hepatic margins
7	No	No	Yes (2)	Cranioventral	Liver and spleen completely obscured
8	Yes	No	Yes (3)	Cranioventral	Indistinct splenic and caudal hepatic margins
9	Yes	Yes	Yes (2)	Cranioventral	Slight loss of clarity of caudal hepatic margin
10	Yes	Yes	No	Cranioventral and mid ventral	Markedly indistinct hepatic and splenic margins.

Table 4.2: The radiological findings in lymphoma patients with peritoneal disease.

Figure 4.1: Lateral abdominal radiograph of a dog with lymphoma showing markedly enlarged sublumbar lymph nodes.

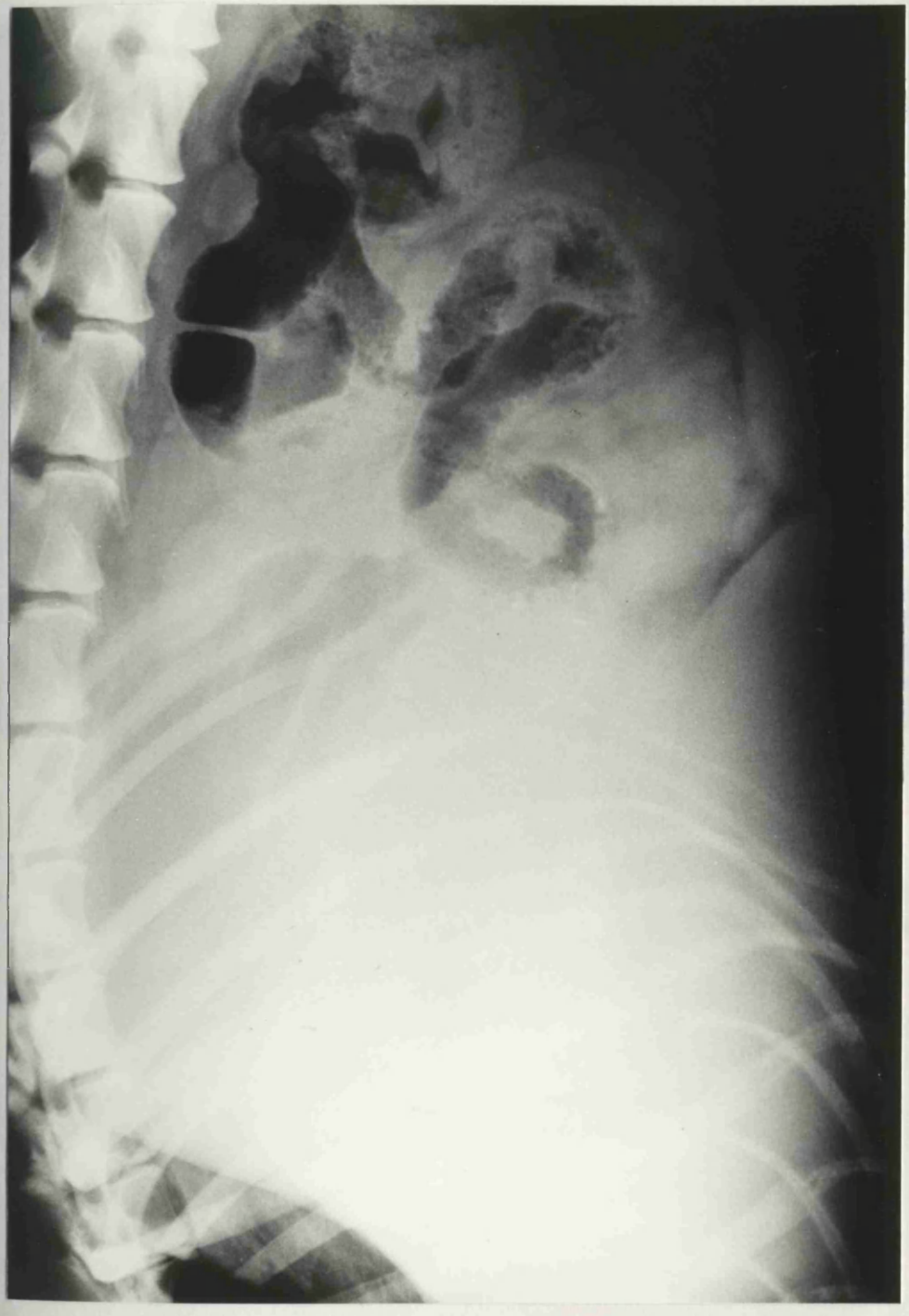


Figure 4.2: Lateral abdominal radiograph of a canine patient with lymphoma showing marked hepatomegaly.

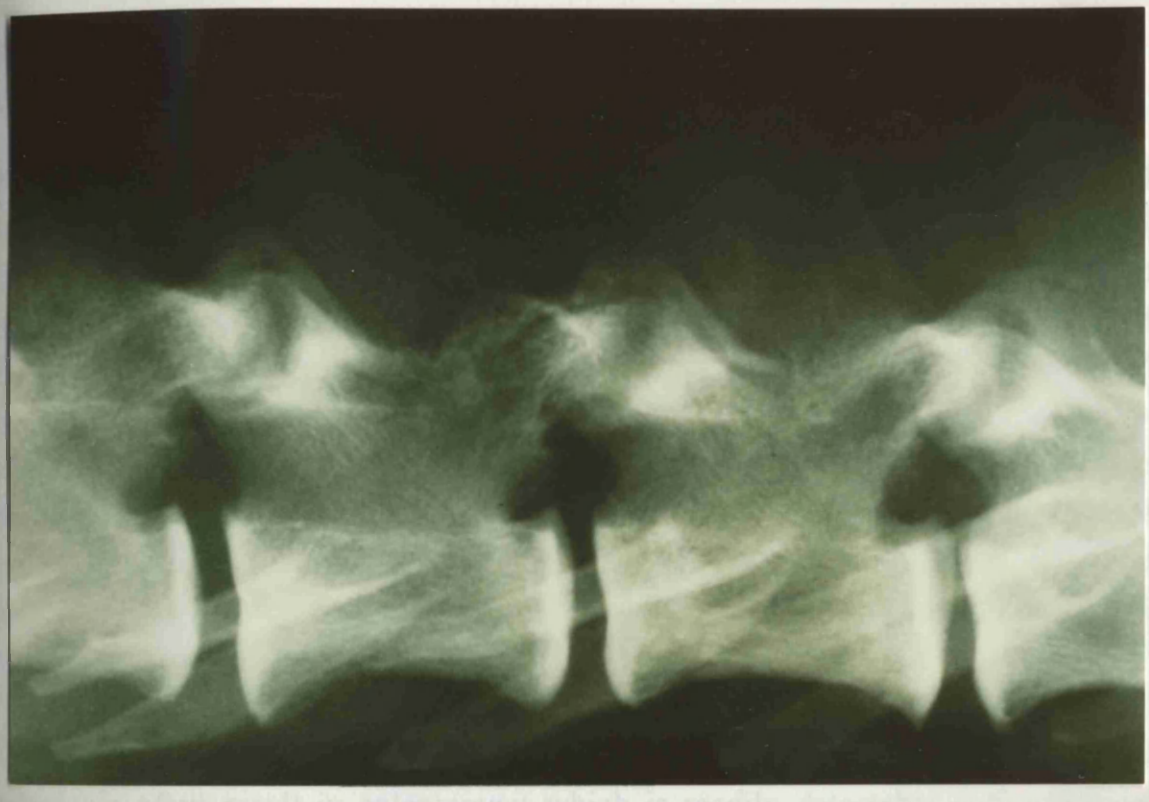


Figure 4.3: Lateral view of the lumbar spine of a dog with lymphoma, showing numerous poorly marginated osteolytic lesions affecting the vertebral bodies, transverse processes and the articular facets.

DISCUSSION OF ABDOMINAL FINDINGS

ABDOMINAL LYMPHADENOPATHY

Radiographic Appearance and Causes of Abdominal Lymphadenopathy

Radiographically, the abdominal lymph nodes can be divided into two main groups: those clustered around the root of the mesentery, seen ventral to the second lumbar vertebra, and those occupying the sublumbar area. It is unusual to be able to see the nodes at the mesenteric root unless these are massively enlarged, as may be seen in some cases of lymphoma (Burk and Ackerman 1986b) or occasionally in mycobacterial infection. Other conditions rarely cause the marked enlargement of these nodes required to allow radiographic detection of lymphadenopathy. Sublumbar lymphadenopathy is more readily recognised, manifesting as an increase in soft tissue density dorsal to the colon as it enters the pelvic canal, causing ventral depression of the fascial plane associated with retroperitoneal fat and of the colon itself.

Changes in the sublumbar nodes due to lymphadenitis or primary or metastatic neoplasia often result in enlargement which is readily detectable radiographically (O'Brien 1978b, Burk and Ackerman 1986b). Under normal circumstances, the nodes in this area form part of the band of soft tissue seen below the caudal lumbar vertebrae and are not readily identifiable without the use of lymphangiographic techniques. The term sublumbar lymph nodes encompasses the medial iliac (located ventral to the fifth and sixth lumbar vertebrae), hypogastric (located ventral to the seventh lumbar vertebra) and sacral/coccygeal lymph nodes (located below the body of the sacrum). The medial iliac node is by far the largest of the group and is a constant finding. Sacral lymph nodes are only seen in about half the canine population. All of these nodes are variable in number (Evans and Christensen 1979).

The medial iliac lymph nodes drain the pelvis, pelvic limb, urogenital system, caudal digestive tract and inguinal lymph nodes. The hypogastric nodes drain the thigh, pelvis, pelvic viscera, tail, lumbar region and sacral nodes, if present. The small sacral nodes receive afferent lymphatics from only adjacent muscle and viscera. The sublumbar lymph nodes are often enlarged as a result of local metastases of neoplasms such as perirectal and rectal carcinomas, prostatic

carcinomas, cystic or urethral carcinomas, other intestinal carcinomas and mast cell tumours involving the hind limbs, perineum or preputial areas (Macy 1985). Sublumbar lymphadenopathy has been reported as a result of metastasis from a bile duct carcinoma (Weaver 1976). Leukaemias and malignant histiocytosis may also cause moderate enlargement of these nodes. Infectious causes of sublumbar lymphadenopathy are also recognised, and this may reflect systemic or local infection. Such lymphadenopathy is seen in some cases of prostatitis.

The mesenteric and colic nodes drain the small intestine (with the exception of the duodenum), pancreas, caecum and colon, and may be enlarged secondary to inflammatory or neoplastic conditions of these visceral organs.

Specific bacterial pathogens associated with abdominal lymphadenopathy include *Actinomyces* and *Mycobacterium*, as well as organisms such as *Brucella*, *Borrelia* and those associated with bacterial endocarditis: the latter conditions tend to be associated with generalised lymphadenopathy. Fungal conditions that are associated with abdominal lymphadenopathy include infection with *Zygomyces*, *Histoplasmosis, Coccidioides*, *Blastomyces* and *Cryptococcus* (Hammer and Couto 1991). However, systemic fungal disease is very uncommon in this country. Several rickettsial organisms may cause lymphadenopathy, but again are rarely a problem in British dogs. In addition, parasitic infections such as demodicosis and leishmaniasis may cause generalised lymphadenopathy. Non-infectious non-neoplastic causes of lymphadenopathy such as autoimmune diseases must be considered, but lymphadenopathy with such conditions rarely results in lymph node enlargement that is appreciable radiographically. This is also the case in most systemic infectious processes, with the exception of fungal granuloma formation.

Enlargement of the sublumbar lymph nodes has a distinctive radiographic appearance which rarely requires differentiation from other dorsocaudal abdominal structures. However, occasionally retroperitoneal haemorrhage may result in the appearance of a soft tissue density in the sublumbar area. This may also occur if there is a tear or rupture of the ureter and urine accumulation in the retroperitoneal space. In contrast to the sharp fairly well circumscribed appearance of the enlarged nodes, haemorrhage or urine accumulation creates a rather diffuse increase in density in this area (Root 1974a). If this is due to a traumatic incident, other evidence of this may be seen radiographically. Rarely, neoplasia extending from the lumbar vertebrae into the sublumbar muscles or arising from the sublumbar muscles may produce either a diffuse or well circumscribed lesion in the sublumbar area which may mimic lymph node enlargement, and may also metastasise to the lymph nodes (Root 1974a).

Enlargement of the mesenteric lymph nodes manifests as soft tissue density in the midcentral abdomen. These masses are usually poorly defined (O'Brien 1978b) and surrounded or obscured by the intestinal mass and are difficult to identify. Renal or ovarian masses will tend to displace the intestinal mass, and in comparison are generally well circumscribed. In man, lymphangiographic techniques and computed tomography are to assess these nodes (Arseneau and Rosenthal, 1980).

Abdominal lymphadenopathy in lymphoma

Enlargement of the sublumbar lymph nodes were identified in 59 of the 79 (75%) of the animals in the current study, and was the most frequently diagnosed abdominal abnormality. The medial iliac nodes were often the most prominent of the sublumbar group, as would be expected as these are the largest nodes in this region. Ackerman and Madewell (1980) similarly found this to be a common abdominal change, but recorded it less frequently, in 42 of the 85 (49%) of the cases they reviewed for which abdominal radiographs were available. Kene (1984) similarly reported sublumbar lymphadenopathy in 13 of the 24 (54%) cases with abdominal radiographs which he reviewed.

The similarity between the results obtained in the two previous studies and the large discrepancy between these and the current study is difficult to explain. It may be that the system of three viewers has increased sensitivity to this change, yet this has not resulted in an increase in sensitivity to other parameters. The 59 cases of sublumbar lymphadenopathy were subdivided further into 13 cases with slight node enlargement, 29 cases with moderate enlargement and 17 cases with marked enlargement. The combined total of cases with node enlargement scores of only 2 and 3 gives a frequency of enlargement similar to that seen in the other studies, and it may be that the group which were awarded a score of 1 contains a number of false positives. In seven of the 13 cases with a score of 1, sublumbar lymph node enlargement was the only identified abdominal abnormality. In addition, the effects of the interpreter being aware of the diagnosis may also have lead to a higher frequency of detection, as the expectation of a positive result prejudices the viewers findings (Garland 1949). It is possible that the cumulative effect of three viewers tending to identify abnormality above normality where there was subtle or equivocal enlargement has lead to an over-diagnosis of this change, which was less evident in the previous studies, as these relied essentially on one viewer [with comparisons to previous reports in the case of Ackerman and Madewell (1980)]. However, Garland (1949) concluded that the increase in positive diagnosis resulting from radiologists expecting change was not accompanied by a significant increase in over-diagnosis. Thus the higher rate of detection in the current study may be a

genuine finding due to either a higher frequency of occurrence of sublumbar lymphadenopathy in the current study group or greater sensitivity to true positives due to the three viewer system.

Enlargement of the sublumbar nodes was the most common solitary abdominal change in both the current study and the review undertaken by Ackerman and Madewell (1980), and was seen in fifteen of 79 and ten of 85 cases respectively.

Enlargement of the mesenteric lymph nodes was identified in only one animal in the present study. In contrast, Ackerman and Madewell (1980) reported this change in 11 of the 85 cases they examined. Additionally, Kene (1984) identified these nodes in the abdomen of four of the 24 cases he reviewed. However, this latter group of patients may also have contained animals suffering from the alimentary form of lymphoma. This discrepancy is difficult to explain. Ackerman and Madewell (1980) report that plain film studies are insensitive to the detection of mesenteric lymphadenopathy, and the awareness of this difficulty may have predisposed the viewer to examine the films carefully for evidence of this change. The latter survey relied essentially on one viewer, and it is recognised that a system of multiple viewers is generally more sensitive to abnormalities so it would be expected that the three viewer system used in the current study would have enhanced appreciation of less readily identifiable changes of this type. This abnormality was not included in the specific parameters selected for review in this study because of the difficulty in identifying these nodes on plain film and because of the apparent infrequency of radiographically demonstrable enlargement of these nodes. This may have reduced the sensitivity of viewers in the current study to this change.

HEPATOMEGALY

The radiographic appearance and differential diagnosis of hepatomegaly

Generalised hepatomegaly is seen in a great many conditions and as such is a very non-specific finding. Non-neoplastic causes of hepatomegaly include fatty infiltration (due to obesity or conditions such as diabetes mellitus), hyperadrenocorticism (where the liver enlarges due to hepatic glycogen accumulation), congestion (e.g. in right sided cardiac failure), hypertrophic nodular cirrhosis (i.e. early cirrhosis with overshooting regeneration), extrahepatic biliary obstruction, diffuse inflammation, amyloidosis, and storage diseases. Regenerative

nodules can also cause marked differences in the size of individual lobes in cirrhotic livers (Suter 1982).

Neoplastic causes of hepatomegaly include lymphoma and leukaemia, haemangioma, haemangiosarcoma, hepatoma, mast cell tumours, hepatocellular carcinoma, bile duct carcinoma and metastatic tumours. Lymphoma is associated with generalised hepatomegaly rather than enlargement of specific lobes or mass lesions, which are more commonly seen in other primary tumours, metastases and benign lesions such as hepatic cysts or abscesses (Root 1974b, O'Brien 1978, Suter 1982). Generalised hepatomegaly is also seen in cases of malignant histiocytosis (Wellman and others 1985, Shaiken and others 1991) and in leukaemia. However, Evans (1987) reports four cases of diffuse liver invasion by cholangiocellular carcinomas, though previous work suggests that, in common with other non-lymphoid primary tumours, these are more commonly seen as a mass lesion (Patnaik and others 1981).

The radiographic appearance of the liver is influenced by characteristics of the patient including conformation, body condition and stage of respiration at time of exposure as well as the size, shape and density of the organ itself. On the lateral projection, the position of the caudal border of the liver varies from just within to just caudal to the last costal arch. The caudal margin should be sharp in outline, tapering to a thin point, but may appear rounded if radiographed obliquely (Root 1974b). On the lateral radiograph this border is formed by the caudal edges of the left lateral and right middle liver lobes. The left lateral lobe moves more caudally in right lateral than left lateral recumbency. In dogs with deep, narrow chests and cranially protruding diaphragmatic cupula, the liver lies within the costal arch and tends not to protrude beyond this at all. In contrast, in dogs with a shallow, broad chested conformation, the diaphragm is relatively flatter and the liver lobes will normally extend a little beyond the costal arch. The liver margin is also projected more caudally at inspiration than expiration.

In obese, pot-bellied dogs, the caudal border of the liver may project beyond the costal arch but the liver will not extend so far dorsally, so that there is a reduction in density in the craniodorsal abdomen on the lateral view (O'Brien 1978c). However, this can be difficult to appreciate. In these dogs, and also aged patients, stretching of the supporting ligaments allows the liver to take up a caudal and ventral position. In addition, conditions which result in over expansion of the rib cage or flattening of the diaphragm due to respiratory difficulty (for example pleural effusion) can cause the hepatic border to protrude beyond the costal arch.

Hepatomegaly manifests itself radiographically in a number of ways (Root 1974ab, Ackerman and Silverman 1977, O'Brien 1978c, Suter 1982). On the lateral view, protrusion of the caudal border beyond the costal arch and caudal displacement of the gastric axis is seen. In addition, the proximal duodenum, right renal shadow and transverse colon may be displaced caudally. On the dorsoventral view, caudal displacement of these structures may be accompanied by displacement towards midline. Diffuse hepatomegaly tends to displace the gastric fundus and body to the left as well as caudally, and if marked also displaces the small intestinal mass caudally. O'Brien (1978c) states that rounding of the caudal borders must be seen before hepatomegaly is diagnosed, but as stated above this may be artefactual if the radiograph is oblique. In addition to rounding of the liver lobes, irregularity of the hepatic margins may be seen and the normal smooth outline lost. Breed conformation, body condition and stage of respiration must also be taken into account.

The radiographic estimation of liver size is thus difficult, and influenced by many characteristics of the patient and technical artefacts (Suter 1982).

In most cases of generalised hepatomegaly, the hepatic margin is smooth in outline. However, irregular, uneven or undulating margins may be seen associated with neoplasia, abscess formation, the presence of a cyst, cirrhosis, or nodular hyperplasia. Although hepatomegaly in lymphoma is usually associated with generalised enlargement with smooth margination, irregular or undulating margins are sometimes seen in advanced cases. Loss of serosal marginal clarity is also seen where there is associated intraperitoneal disease, such as ascites.

Hepatomegaly in lymphoma

Hepatomegaly was seen in 42 of the 79 (53%) cases in the present study and similarly in 40 of the 85 (47%) cases reviewed by Ackerman and Madewell (1980). In both studies, this abnormality was rarely seen alone and was associated frequently with splenomegaly and/or sublumbar lymphadenopathy. In addition, Kene (1984) reviewed the abdominal films of 24 dogs with lymphoma, and found that 14 (58%) of these had hepatomegaly, and recorded that nine cases had concomitant splenomegaly. Thus it has been found consistently that hepatomegaly is a common radiographic feature of lymphoma patients. Ackerman and Silverman (1977) state that hepatomegaly seen in association with splenomegaly, renal enlargement or enlarged sublumbar lymph nodes is highly suggestive of lymphoma, but caution must be exercised and the diagnosis must be supported by the clinical and laboratory data. The findings of the present study support this approach.

In the study undertaken by Ackerman and Madewell in 1980, two of the 85 dogs had hepatomegaly as the only radiographic abnormality identified. In the current study, five such case were recorded. It is possible that some of these animals represent false positives due to the technical and patient factors discussed above. However, Valli (1993), states that the liver is involved in virtually all cases of lymphoma on histopathological examination, and that this organ is often involved more extensively than the spleen. Thus it is reasonable to expect that hepatomegaly may be detectable radiographically in some cases before splenomegaly is evident, or in the absence of radiographic involvement of other abdominal organs.

Neither Ackerman and Madewell (1980) nor Kene (1984) commented upon the nature of the hepatic margin in cases where they recorded hepatomegaly. In most cases of hepatomegaly in the current study the caudal border of the liver was rounded but retained a smooth outline. Occasionally, an undulating or irregularly uneven outline was seen. This type of change may reflect multifocal rather than truly diffuse disease or architectural disruption due to marked infiltration. Less frequently, the caudal border protruded well beyond the costal arch but tapered to a sharp point. In these cases, it is possible that stretching of the supporting ligaments of the liver had allowed the liver to take up a more caudoventral position, but there was no obvious reduction in density in the craniodorsal abdomen to support this change of position. It was also noted incidentally when selecting the films for the study that in some cases which had a smooth hepatic outline at the time of presentation this later became undulating or uneven when the dog relapsed and the disease progressed.

O'Brien (1978c) confirmed that lymphoma is a very common cause of hepatomegaly, often seen with accompanying renal enlargement. While hepatomegaly was a common finding in the current study, there were no reported cases of renal enlargement. Ackerman and Madewell (1980) reported only one dog with renal enlargement in a study group of 85 dogs, 40 of which had hepatomegaly. Although Kene (1984) reported two cases with renal enlargement within a group of 24 patients suffering from lymphoma of any form, concurrent hepatomegaly was not mentioned. Thus it appears renal enlargement is seen infrequently in association with hepatomegaly in dogs with multicentric lymphoma, and is in itself an uncommon radiological abnormality in this disease.

SPLENOMEGALY

The radiographic appearance of splenomegaly

The spleen is the largest single component of the reticuloendothelial system, and constitutes a major source of reticuloendothelial and immunogenic cells in the body. It is interposed directly between the portal and systemic circulation. It is worth noting that the spleen has no afferent lymphatics, and that infiltration by cells in lymphoma occurs only via the haematogenous route.

The spleen is a very dynamic organ, and changes markedly in size as a physiological response to a variety of states, making radiographic diagnosis of significant splenomegaly imprecise and rather difficult. The many functions of the spleen include haematopoiesis, filtration, phagocytosis, and its roles in immunogenic processes and as a blood reservoir. Although bone marrow is the principal site of haematopoiesis in post-natal dogs, the spleen retains the potential to perform this function should the need arise (Couto 1989).

Generalised splenomegaly may be due to a number of non-neoplastic causes, including physiologic response, passive congestion, inflammatory disease (splenitides of various aetiologies), hyperplastic splenomegaly (often associated with immune mediated disease), extramedullary haematopoiesis, and splenic torsion (Couto 1985). Very rarely, non-neoplastic infiltration of the spleen occurs in amyloidosis or storage diseases, producing organ enlargement. Splenomegaly is also seen as a result of drug administration: phenothiazine tranquillizers and barbiturates induce splenomegaly by smooth muscle relaxation. This is often marked: pooling of blood in an enlarged spleen under anaesthesia can account for up to 30% of the blood volume (Barton 1981). The appearance is of generalised splenic enlargement with clearly defined margins.

Infiltration of the spleen with neoplastic cells is one of the commonest causes of splenomegaly in small animals (Couto 1985). Splenic infiltration by neoplastic cells occurs most frequently via the haematogenous route, resulting in a significant increase in organ dimensions with complete obliteration of the normal organ architecture at the cellular level. Diffuse splenomegaly due to infiltration by non-haematopoietic neoplasms is rare in the dog (Couto 1989). Marked splenomegaly is seen in acute and chronic leukaemias, lymphoma, systemic mastocytosis, some types of malignant histiocytosis and malignant myeloma (Couto 1985, Pope and

Rochat 1993). Metastatic neoplasms, myelofibrosis, and polycythaemia vera may also cause infiltrative splenomegaly.

Necrotising splenitis has been reported in association with lymphoma (Ridgeway and others 1978, Couto 1989). There had been no recorded radiographic signs of this lesion in the case reported by Ridgeway and others (1978).

Changes in the shape and outline of the spleen may result from mass lesions or healed fractures of the spleen, and this type of splenic rupture and haematoma formation have been reported in lymphoma cases (Couto 1985, Wrigley and others 1988). However, the most commonly seen solitary masses are haemangioma, haemangiosarcoma, haematoma, leiomyosarcoma, or abscesses. Rarely, splenic mass lesions have been seen in malignant histiocytosis (Shaiken and others 1991). In addition, nodular hyperplasia results in multiple small nodules, which may give the spleen an irregular or uneven outline: this is seen in some older dogs.

Radiographically, the size and position of the spleen are more variable on the lateral projection than on the dorsoventral or ventrodorsal (Ackerman and Silverman 1978). In this view, it is the body and the tail of the spleen which are visualised. The head of the spleen is relatively fixed (to the left side of the gastric greater curvature by the gastrosplenic ligament) but both the body and the tail are comparatively mobile, and are also subject to greater fluctuations in size than the head (Root 1974a, Ackerman and Silverman 1978). On the lateral view, the triangular shadow created by the body and tail may be situated far cranially in the infrasternal fossa, where it may be difficult to distinguish from the liver, or may be seen caudal to the umbilicus. Diffuse splenomegaly is recognised radiographically not only by an increase in size but also by a rounding of the borders of the splenic shadow (Root 1974a).

It is important to consider that splenomegaly in leukaemia patients and lymphoma cases with marrow involvement may be due at least in part to extramedullary haematopoiesis as well as neoplastic infiltration.

Splenomegaly in multicentric lymphoma

Splenomegaly was observed in 36 of the 79 (46%) cases reviewed in the current study. This change was never seen as a solitary abnormality. A number of these animals had been sedated with phenothiazine derivatives for radiographic examination, and some were anaesthetised. Full details of sedation or anaesthesia were not available for all patients, so it was impossible to divide these animals into

subpopulations where drug administration may or may not have been responsible for splenomegaly. Ackerman and Madewell (1980) reported that splenomegaly was the commonest abdominal radiographic finding. This abnormality was seen in 47 of the 85 (55%) cases Ackerman reviewed, and in six of these cases was the only abdominal radiographic finding. There is no mention made of physical or chemical restraint methods for the patients, so it is possible that some of these animals had received phenothiazine tranquillizers or barbiturates. Kene (1984) reported 13 cases of splenomegaly in his review of 24 (54%) cases. Again, there is no information given on chemical restraint of the patients for radiographic examination.

Most of the patients within the survey group were in moderate to obese body condition, so that the serosal margins of the enlarged splenic shadow were readily visible. Loss of serosal margin visualisation due to intraperitoneal disease can result in blurring of the splenic margins. Extracapsular extension of the pathological process is often responsible for indistinctness of the splenic margin and for the appearance of localised peritonitis or ascites (McNeel 1987). While transcoelomic spread is not generally associated with lymphoma, local transudation may occur in infiltrative disease. Of the ten animals reported to have ascites in the current study, eight had indistinct splenic margins, and in five of these cases the splenic shadow was obscured partially by the fluid (i.e. the ventral margin was not clearly visible). In one case the splenic outline was completely obscured. Ackerman and Madewell (1980) report that the splenic outline could not be discerned because of the concurrent presence of ascites in four of the 85 cases they reviewed.

It is clear from all these results that splenomegaly is a common finding in cases of lymphoma, but that a study which precludes the use of phenothiazine tranquillizers or barbiturates would be required to estimate the true frequency of the abnormality. Also, it must be remembered that in some cases splenomegaly is at least in part due to extramedullary haematopoiesis stimulated when the marrow cannot keep up with demand for blood cell production, for example in myelophthesis and less commonly where there is tumour associated autoimmune haemolytic anaemia or thrombocytopaenia.

ASCITES/PERITONEAL DISEASE

Peritoneal fluid accumulation may occur in many disease situations. Exudative effusions may be caused in a variety of infectious causes, and also by non-microbial irritants such as bile or urine. Transudates may become exudative in time due to

the induction of inflammation by components of the fluid. There are many causes of transudative effusions, including chronic liver disease, hypoproteinaemia associated with protein losing enteropathy or glomerulonephropathy, post-hepatic venous hypertension (for example, in right sided heart failure), and intra-abdominal neoplasia (especially lymphoma, ovarian neoplasia, and acinar pancreatic carcinoma) (Prasse 1992).

Both primary and secondary tumours of the peritoneum are uncommon in the dog. Peritoneal mesotheliomas are associated with fluid production. Secondary tumours reach the peritoneum mainly by direct implantation, and this is seen much more commonly in carcinomas then sarcomas (Barker 1993). Spread to the peritoneum by ovarian tumours, bile duct carcinomas and pancreatic adenocarcinomas has been described. This may mimic peritonitis and there may be associated ascites.

Radiographically, peritoneal fluid causes a loss of detail which obscures the abdominal viscera. This may be localised or diffuse, depending on the volume present. As most diseases which affect the peritoneum can cause effusion by inflammation or irritation (Root and Lord 1971), small volumes of fluid may result from localised involvement of the peritoneum in a variety of disease processes.

Evidence of intraperitoneal disease was seen infrequently in the current study, affecting only ten of the 79 cases. In the majority of cases, the changes were restricted to the cranioventral abdomen, where there was a localised loss of detail. The splenic shadow and caudal border of the liver remained visible in most cases, though the margins appeared indistinct or blurred. These changes are typical of low volume effusions, localised peritonitis or abdominal carcinomatosis, rather than large amounts of peritoneal fluid. However, much of the radiographic appearance of peritonitis and carcinomatosis is due to the fluid produced by the peritoneum (especially the visceral peritoneum) in response to the changes occurring within this serous membrane.

Root and Lord (1971) described the radiographic appearance of peritoneal carcinomatosis in dogs and cats. This change was associated with peritoneal and serosal spread of carcinomas, but can appear similar to the changes seen in lymphoma. Carcinomatosis often affects the cranioventral abdomen preferentially, and manifests as a diffuse, patchy or irregularly nodular pattern. These authors state that this cannot be differentiated radiographically from peritoneal fluid accumulation associated with lymphoma. Transcoelomic spread as such is not generally associated with lymphoma. Local miliary spread of splenic or hepatic haemangiosarcomas can also give a similar mottled or nodular appearance, but often

haemorrhage from the primary mass or metastases produces a haemoperitoneum which masks these changes. In addition, the pattern seen in lymphoma is similar to that seen in any localised peritonitis, and the distribution of the change is such that pancreatitis must be included as a differential diagnosis in many cases. Other causes of localised peritonitis may present with additional radiographic findings such as free gas within the peritoneum or a mass lesion representing a hepatic or splenic abscess. Occasionally, a wet hair coat can also produce an artefactual localised area of loss of detail and increased density (O'Brien 1978a).

In contrast to the changes seen in the current study, in four of the five cases recorded by Ackerman and Madewell (1980) to have radiographic evidence of ascites the splenic outline was completely obscured by the fluid present within the peritoneal cavity. No comment is made as to other problems of interpretation resulting from the presence of free peritoneal fluid, which suggests that the ascites was localised cranioventrally or midventrally. It seems unlikely that the hepatic shadow was clearly visible in these cases, but this is not discussed. Thus it appears volumes of fluid seen by Ackerman and Madewell (1980) were in general larger than those seen in the current study, where in most cases the hepatic and splenic shadows were discernible. Kene (1984) saw free peritoneal fluid in one of the 24 cases he reviewed, and makes no comment on its distribution or any features obscured by its presence.

Ascites as a solitary abdominal finding is uncommon. This change was seen in only one case in the current study, and the liver and spleen could be identified. In three of the 85 cases reviewed by Ackerman and Madewell (1980) ascites was the only recorded change. However, in the latter study the larger volumes of fluid prevented diagnosis of other changes.

The appearance of ascites in lymphoma patients thus varies from subtle mottling around the margins of the liver or spleen to the accumulation of moderate to large volumes of fluid. Radiographically, small volumes of fluid must be differentiated from peritoneal carcinomatosis or localised peritonitis. In these cases, where the liver and spleen can still be identified, changes in these organs or abdominal lymphadenopathy may alert the radiologist to the possible diagnosis of lymphoma. However, when there is a moderate to large amount of fluid present, the other changes frequently associated with lymphoma may be impossible to visualise. In this situation, abdominal ultrasonography may help support a provisional diagnosis of lymphosarcoma (Lamb and others 1991) but cytological or histological confirmation will still be required.

ULTRASONOGRAPHIC EVALUATION OF THE LIVER AND SPLEEN

The information which a plain radiograph can provide about a diseased liver or spleen is limited. Although radiographs will demonstrate changes in the shape, size and position of these organs they often give no indication of the disease process which is causing the change, or the nature of the intraparenchymal change. For example, where hepatomegaly is due to an infiltrative disease process such as lymphoma, there may be no other abdominal radiological abnormalities to help reduce the long list of differentials for organomegaly. Even in the presence of more than one abnormality, radiographs cannot provide a definitive diagnosis. Additionally, where there is peritoneal fluid accumulation, the abdominal organs may be obscured. For these reasons, ultrasonographic evaluation is used increasingly to identify and investigate abnormalities such as hepatomegaly and splenomegaly, in an attempt to increase the specificity of the findings without resorting to invasive techniques. This technique can elucidate whether the observed splenomegaly or hepatomegaly is due to infiltration or congestion, whether the pathology is truly diffuse or a multifocal change, and whether mass lesions are present which were not recognised radiographically.

Ultrasound evaluation of the spleen can be extremely helpful in evaluating the nature of splenic enlargement (Couto 1985). However, the ultrasonographic patterns seen are non-specific. The typical "plum-pudding" appearance of multiple hypoechoic areas surrounded by tissue of variable echogenicity associated with haemangioma and haemangiosarcoma has also been seen frequently in lymphoma (Wrigley and others 1988, Dennis 1991, Lamb and others 1991). Wrigley and others (1988) also report the presence of smaller poorly marginated hypoechoic nodules which are difficult to identify without high-resolution transducers. Occasionally anechoic, hypoechoic or hyperechoic mass lesions are seen in lymphoma, or there may be a diffuse reduction in echogenicity or irregularity of the splenic border (Wrigley and others 1988, Lamb and others 1991). In some cases, the mass lesions may represent haematomas which develop secondary to lymphomatous erosion of the splenic vessels. Wrigley and others (1988) recorded hypoechoic or anechoic nodules in all 12 selected spleens examined, in various combinations with the other features described above, while Lamb and others (1991) saw ultrasonographic changes in five of six cases of lymphoma involving the spleen. Thus ultrasonography appears to be fairly sensitive to the changes associated with splenic infiltration in lymphoma, though the findings again are supportive or suggestive of a diagnosis rather than confirmatory.

Ultrasonography allows easy differentiation of hepatomegaly due to congestion and organ enlargement due to infiltrative disease. In addition, fatty or fibrous infiltration tends to produce a hyperechoic pattern, rather than the hypoechoic pattern seen commonly in lymphoma (Dennis 1991). Nyland (1984) identified three patterns in canine lymphoma. The patterns described were mild diffuse hypoechogenicity, multiple poorly marginated anechoic or hypoechoic lesions and multiple, round echodensities with a surrounding area of sonolucency ("target lesions"). The pattern of multiple hypoechoic lesions must be differentiated from haemangioma and haemangiosarcoma. Additionally, intraparenchymal mass lesions may occur in lymphoma (Nyland 1988, Dennis 1991, Lamb and others 1991) and these may have a similar appearance to abscesses, other tumours, regenerative nodules and cysts. Wrigley and others (1988) also identified focal hypoechoic lesions in dogs with lymphoma, as well as patchy areas of hypoechogenic parenchyma and diffuse hypoechogenicicty. However, the liver parenchyma may appear normal in lymphoma patients, though hepatomegaly is detected ultrasonographically. When ultrasound examination detects abnomalities, the lesions identified are non-specific. Lamb and others (1991) detected hepatic abnormalities in only three of 14 cases with hepatic infiltration by lymphoma, and thus concluded that this is an insensitive method of investigation. This is partly because diffuse changes in echogenicity are difficult to appreciate, and this problem is compounded where there is concomitant splenic involvement and reduction in the echogenicity of this organ (Wrigley and others 1988).

In conclusion, ultrasound may give additional support to a tentative diagnosis of lymphoma, or suggest this diagnosis but, like radiology, the findings are non-specific and diagnosis relies on cytological or histopathological confirmation. Ultrasonographic examination is relatively sensitive to splenic parenchymal change in lymphoma. In contrast, this technique is of variable sensitivity in the detection of hepatic lymphoma, and may show no abnormalities within an affected organ. However, ultrasound can be very valuable in assessing the liver and spleen in cases where the presence of ascites precludes radiographic identification of these organs.

OTHER FINDINGS

Bony change

In one case in the current study, there was radiographic evidence of bone involvement in the neoplastic process. This manifested as numerous rather poorly

defined areas of osteolysis in the lumbar vertebral bodies and transverse processes and erosive poorly marginated osteolysis around the articular facets in this area (Figure 4.3, page 65). There was no accompanying sclerosis. Kene (1984) recorded focal radiolucencies affecting the lumbar vertebrae and ilia in one case as a finding on review of the abdominal radiographs of 24 cases of lymphoma. This author also recorded abnormalities in the ribs and spinous processes of five dogs, including fractures, but this is not expanded upon and the precise nature of these lesions is unclear. Radiographic evidence of bony involvement was not recorded in the survey of 100 cases undertaken by Ackerman and Madewell in 1980.

Although lymphoma may involve the bone marrow, this tumour rarely causes sufficient bone destruction to produce radiographically visible lesions. When detectable bony lesions occur, they often involve the vertebrae and pathological fractures may result (Shell and others 1989, Pool 1990). In addition, lymphoid lesions have been reported in the diaphyses and distal metaphyses of long bones, ribs, skull, pelvis and patella (Turnwald 1988, Ogilvie and others 1989, Rogers and others 1989, Shell and others 1989, Pool 1990). These lesions are generally osteolytic without accompanying periosteal new bone or marked soft tissue swelling This type of pattern is also seen in the metaphyses of long bones associated with poorly differentiated histiocytic tumours (Pool 1990, Palmer 1993). The main differential diagnoses of multiple focal lytic areas without accompanying sclerosis, as identified in the current study, are multiple myeloma and metastatic neoplasia. Lymphoma has also been associated with multiple sclerotic medullary densities with a polyostotic distribution (Morgan 1974, Dennis 1991).

SUMMARY OF ABDOMINAL FINDINGS

There are a number of points which can be made regarding the abdominal radiographic abnormalities seen in canine patients with multicentric lymphoma. This disease cannot be diagnosed on the base of the radiographic findings alone, though in some cases the findings are highly suggestive. Some animals show no radiographic evidence of disease, and when abnormalities are seen they are often non-specific findings. It is unusual to identify a solitary abdominal abnormality in this disease. Sublumbar lymphadenopathy, hepatomegaly and splenomegaly are the most frequently identified radiological features. In the current study, sublumbar lymphadenopathy is seen more commonly than any other abnormality but other work would suggest that the frequency of occurrence of each abnormality is similar (each affecting around half of all patients).

Radiographically, sublumbar lymphadenopathy is readily detectable, and although not specific for lymphoma, is commonly seen. However, the mesenteric lymph nodes are difficult to identify on plain films, even when enlarged, and are recognised much less frequently. Hepatomegaly is a relatively common but non-specific finding, and many factors affect the radiographic appearance of the liver. Similarly, splenomegaly is seen commonly but can be caused by a myriad of conditions. Organomegaly affecting the liver and the spleen therefore may not always reflect involvement in the primary disease. However, hepatomegaly and splenomegaly are often seen together in lymphoma patients and the concurrent presence of both these abnormalities should alert the radiologist to this possible diagnosis. Where sublumbar lymph node enlargement is also present, these changes are very suggestive of a diagnosis but by no means pathognomonic.

Ascites or peritoneal disease is recorded less frequently in lymphoma patients. Where the volume of fluid is small, the changes may mimic localised peritonitis or carcinomatosis in the cranioventral abdomen, around the liver and spleen. Where the volume of fluid is large, much of the abdominal viscera, including the liver and spleen, may be obscured so little information can be gained from the radiograph. Thus the presence of fluid only serves to confuse the radiological picture.

CHAPTER 5.

HYPERCALCAEMIA AND THORACIC RADIOLOGICAL ABNORMALITIES

RESULTS

Plasma calcium levels at presentation were available for 78 of the 84 patients with thoracic radiographs (Appendix 1.c, pages 114-117). These values were based on blood samples taken on the day of or the day prior to radiography, before the administration of chemotherapy or fluid therapy. All calcium values have been adjusted retrospectively with respect to the plasma albumin levels. Only eight of the 78 (10%) patients were hypercalcaemic, defining this as a plasma calcium value of greater than 3.00 mmol/l.

Of the eight hypercalcaemic patients, four were entire male and four were entire female. The age of patients ranged from 2.6 to 11.4 years, the mean being 6.3 years. This age distribution is thus similar to that of the study group as a whole. All eight of these patients showed systemic signs of illness consistent with the hypercalcaemia.

The thoracic radiological findings for these eight cases are summarised in the Table 5.1 (page 84). It is interesting to note that two of these dogs had evidence of intercurrent disease on initial abdominal radiographs which was found to be due to a second neoplastic process. In one of these cases, there was prostatomegaly as a result of a prostatic adenocarcinoma. In the second there was marked enlargement of the sublumbar lymph nodes, affecting the medial iliac node predominantly. This mass continued to increase gradually in size while the animal was in remission and at post mortem the enlarged nodes were found to be replaced completely by sheets of adenocarcinomatous cells. Although this node is a common site of metastasis of adenocarcinomas arising from the apocrine glands of the anal sacs no primary neoplasm was found at this site. Dog 7 is also exceptional, being the only animal within the survey group which showed osteolytic lesions (Figure 4.3, page 65). These affected the lumbar spine and were seen as irregular poorly marginated areas of increased lucency within the vertebral bodies and transverse processes, and around the articular facets.

Three of the hypercalcaemic animals had severely compromised renal function at the time of presentation, and did not respond to symptomatic treatment. Although hypercalcaemia can lead to renal damage which is reversible in the first instance it can ultimately result in a severe and irreversible nephropathy (Kruth and Carter 1990). Two of these cases were also exhibiting central neurological signs.

Patient	Age (years)	Sex	Stage	Adjusted calcium (mmol/l)	Suprasternal lymphadenopathy (score)	Tracheobronchial lymphadenopathy (score)	Cranial mediastinal lymphadenopathy	Thymic infiltration	Pulmonary infiltration	Pleural change
1	5.0	M	III (b)	4.70	Yes (2)	Yes (1)	Yes	Yes	No	No
2	7.7	F	IV (b)	4.57	No	Yes (1)	No	No	No	No
3	11.4	F	V (b)	3.94	No	No	No	No	No	No
4	7.1	M	V (b)	3.96	Yes(1)	No	No	No	No	No
5	3.5	M	V (b)	3.92	No	No	No	No	No	No
6	5.0	M	II (b)	4.10	No	No	No	No	No	No
7	8.0	F	V (b)	3.65	No	No	No	Yes	No	No
8	2.6	F	III (b)	3.72	Yes (1)	Yes (2)	No	No	No	No

Table 5.1: Patient details, serum calcium values and thoracic radiological findings of eight hypercalcaemic lymphoma patients.

DISCUSSION

Serum calcium values

Total serum calcium is made up of protein-bound calcium (50%), ionised calcium (10%) and complexed calcium (40%) (Chew and Meuten 1982). Only the ionised calcium is biologically active, i.e. available for extracellular function and activity. In 1982, Meuten and others demonstrated a positive linear relationship between total calcium and albumin from which they derived a formula used to adjust the total calcium values relative to serum albumin levels. This formula is given below. In addition, their findings illustrated that adjustment of total calcium relative to plasma proteins was essential to avoid overlooking hypercalcaemia in hypoproteinaemic or hypoalbuminaemic patients where the low level of protein bound calcium is compensating for the increased ionised calcium to give a total calcium value within the normal range.

Adjusted calcium(mg/dl) = 3.5 - albumin(g/dl) + measured calcium(mg/dl)

The units used in the University of Glasgow Veterinary Hospital for calcium are mmol/l: these are converted into mg/dl by multiplying by 4. The units for albumin are g/l: these are converted into g/dl by dividing by a factor of 10 (Meuten and Armstrong 1989.)

Causes of hypercalcaemia

Malignant tumours have been recognised as the most common cause of hypercalcaemia in the dog (MacEwen and Siegel 1977, Chew and Meuten 1982, Weller 1984, Elliott and others 1991). Lymphoproliferative diseases are the most frequently reported cause of this paraneoplastic syndrome (Weller and others 1982b, Norrdin and Powers 1983, Wootton and Pearson 1988, Elliott and others 1991), with multicentric lymphoma the most common form of lymphoproliferative disease associated with hypercalcaemia (Weller and others 1982b, Elliott and others 1991). As multicentric lymphoma is the commonest form of lymphoproliferative disease in the dog this is to be expected. In man, this paraneoplastic syndrome is reported to occur frequently in a variety of malignancies, including leukaemia and lymphoma, lung tumours, some tumours of the urogenital system, oesophageal and colonic cancers (Gardner 1968, Brown 1981). The true incidence in veterinary patients is unknown. Various authors estimate the incidence of this syndrome in

canine lymphoma to be between 10 and 33% (MacEwen and Siegel 1977, Weller and others 1982a, Couto 1989, Kruth and Carter 1990).

A number of other tumours have been associated with hypercalcaemia in the dog. After lymphoma, apocrine adenocarcinoma of the anal sac is the commonest neoplastic cause, followed by multiple myeloma. Meuten and Armstrong (1989) concluded that these three malignancies probably account for more than 98% of dogs with hypercalcaemia and malignancy. Primary adenoma/carcinomas of the parathyroid gland are also associated with this syndrome, as are primary bone tumours and metastases to bone. Additionally, hypercalcaemia associated with lymphoid leukaemia and various solid neoplasms have been described (Brown 1981, Weller 1984 and 1985, Elliott and others 1991, Dobson and Gorman 1991). These neoplastic conditions are summarised in Table 5.2 (page 87).

System/site	Neoplasm
Lymphoid tissue	LYMPHOMA
	Lymphoid leukaemia
	Multiple myeloma
	Thymoma
Skin and Soft Tissue	ADENOCARCINOMA OF THE APOCRINE GLANDS OF THE ANAL SAC
	Squamous cell carcinoma
	Fibrosarcoma
Abdominal Cavity	Gastric carcinoma
	Adenocarcinoma of the exocrine pancreas
	Metastatic adenocarcinomas of unknown origin
Respiratory system	Epidermoid carcinoma
	Nasal adenocarcinoma
	Primary lung tumours
Urogenital System	Interstitial cell tumour
	Seminoma
	Bladder tumour
Mammary Glands	Adenocarcinoma
Endocrine Glands	Parathyroid adenoma/adenocarcinoma
	Thyroid adenocarcinoma
Skeletal system	Primary bone tumours
	Metastatic bone tumours

Table 5.2: Neoplasms associated with hypercalcaemia in the dog.

It is probable that the hypercalcaemia exhibited by the dog with adenocarcinomatous infiltration of the sublumbar nodes (patient 2) was due primarily to this lesion rather than malignant lymphoma, as hypercalcaemia continued to be a problem even when the lymphoma was in complete clinical remission. It is generally recognised that hypercalcaemia associated with malignant lymphoma will abate with chemotherapeutic treatment, though recurrence often accompanies relapse (MacEwen and Siegel 1977, Meuten and Armstrong 1989). Unfortunately, the primary lesion in this case was not identified even at post-mortem (the dog was ultimately euthanased due to a metastasised hepatic haemangiosarcoma rather than either of the former neoplasms). It is also possible the prostatic adenocarcinoma in dog 6 was contributing to the hypercalcaemia.

Non-malignant causes of hypercalcaemia include hyperadrenocorticism, primary renal failure, osteomyelitis, hypervitaminosis D, and osteopaenia due to disuse (Chew and Meuten 1982, Elliott and others 1991). Of these, hyperadrenocorticism is the most common. Hyperproteinaemia, hyperlipaemia or laboratory error can also elevate this parameter. Hypercalcaemia is seen very occasionally in cases of severe hypothermia. It is important to note that young growing animals have been shown to have elevated calcium, but this is generally below 3.5 mmol/l (Chew and Meuten 1982). Elliott and others (1991) also report one case of chronic panniculitis with hypercalcaemia which resolved on treatment of the dermatological problem.

Cranial mediastinal disease and hypercalcaemia

Some authors have proposed an association between cranial mediastinal disease and hypercalcaemia in lymphoma patients (Chew and Meuten 1982, Wootton and Pearson 1988, Meuten and Armstrong 1989). The findings of this study do not support this: cranial mediastinal disease did not occur in most dogs with lymphoma which were hypercalcaemic. Thirty eight of the 78 (49%) animals in the current study group for whom serum calcium values were available showed evidence of cranial mediastinal disease i.e. suprasternal or cranial mediastinal lymphadenopathy, or thymic enlargement, and only four of these patients were hypercalcaemic. The remaining four hypercalcaemic dogs had no evidence of a cranial thoracic mass. Weller and others (1982b) and Elliott and others (1991) also dispute the statement that most hypercalcaemic animals have cranial mediastinal disease. In a series of 24 animals with hypercalcaemia associated with lymphoma, Weller and others (1982b) found only one case where there was cranial mediastinal widening. In addition, these authors stated that the radiographic findings in that series of patients did not differ from those reported by Ackerman and Madewell (1980). Thus it appears that the presence of cranial mediastinal disease is neither a prerequisite for nor a very frequent finding in hypercalcaemic lymphoma patients.

The lack of clarity regarding the relationship between cranial mediastinal disease and hypercalcaemia in canine lymphoma is due, at least in part, to the fact that most of the investigations have not differentiated animals where there is cranial mediastinal involvement from animals where the thymus is the site of origin of the tumour. This has lead to comparisons being made between groups where there is evidence of cranial mediastinal nodal involvement in multicentric disease and groups where at least some of the patients suffered from the thymic form of lymphosarcoma, which is also referred to as the cranial mediastinal form.

However, two of the six animals with thymic enlargement in the current study were hypercalcaemic, suggesting that perhaps animals with thymic involvement are more likely to be hypercalcaemic than those in which this organ is unaffected. As most lymphomas associated with humoral hypercalcaemia of malignancy are of T cell origin, and most lymphomas associated with normocalcaemia are of B cell origin (Capen 1993), this is not an unreasonable proposition. It must be considered that these two patients had multicentric involvement of a T-cell tumour of thymic origin, rather than thymic involvement in the multicentric form.

Bone involvement in hypercalcaemia

The bone changes associated with hypercalcaemia of malignancy are usually subtle, reflecting alterations in bone remodelling activity and are generally not recognised clinically (Norrdin and Powers 1983). Such lesions would rarely be visible radiographically: 30% bone demineralisation may result in suspicion of reduced bone density radiographically, but this osteopaenic appearance is only readily appreciated after 50% demineralisation (Kealy 1979, Morgan 1981). The exception to this is the situation where there is metastasis to or direct involvement of the skeleton, where localised osteolysis may be seen. Patient number 7 has osteolytic lesions which may have been associated with the development of hypercalcaemia. There was evidence of bone marrow involvement in this case on bone marrow aspiration. There were no radiographically visible skeletal lesions in the other six cases. Although bone metastasis is a common cause of hypercalcaemia in man, this is not the case in the dog (MacEwen and Siegel 1977). It has been proposed that bone marrow involvement is a requirement for the development of hypercalcaemia (Meuten and others 1983). Norrdin and Powers (1983) suggested that the hypercalcaemia seen in lymphoproliferative disease is mediated by a humoral factor, and also stated that bone marrow involvement is not essential for hypercalcaemia to develop. This view is supported by Weller and others (1982b), who found evidence of marrow involvement in only two of ten cases for which detailed pathological findings were available. Bone marrow aspiration cytology results were only available for one hypercalcaemic animal in the current survey (dog 7): this case did have bone marrow involvement, and also osteolytic lesions as described above.

CHAPTER 6.

THE PROGNOSTIC RELEVANCE OF THE RADIOLOGICAL FINDINGS AND CLINICAL STAGING OF LYMPHOMA PATIENTS

FACTORS AFFECTING PROGNOSIS

Treatment schedules

Fourteen of the animals within the selected group of 84 received no chemotherapy, either because of the poor prognosis for return to good quality of life or at the request of the owner. The remainder of the animals were treated.

The two standard protocols used in the hospital during this period are given below (Tables 6.1, below and Table 6.2, page 92). However, there were many cases where animals were transferred form one protocol to the other either at first relapse or occasionally due to complications of chemotherapy. The drugs used in the standard protocols were epirubicin ("Pharmorubicin", Farmitalia Carlo Erba, St. Albans), cyclophosphamide ("Endoxana", Asta Medica Ltd, Cambridge); vincristine sulphate (David Bull Laboratories, Warwick) and prednisolone (Kerfoot Pharmaceuticals, Ashton-Under-Lyme). In addition, several animals were treated with L-asparginase ("Erwinase", CAMR, Salisbury) or doxorubicin (Farmitalia Carlo Erba, St. Albans) on relapse. Chlorambucil ("Leukeran", Wellcome Medical, Crewe) was used in place of cyclophosphamide when cystitis occurred. Thus protocols were modified to suit the individual patient. The dosages of drugs not listed in the standard protocols are given in Table 6.3 (page 92).

Induction and Maintenance	
Epirubicin	30 mg/m^2 intravenously (reduced to 25 mg/m^2 in later cases) every 21 days
Prednisolone	40 mg/m^2 per os daily for seven days, then 20 mg/m^2 every other day
Cyclophosphamide	50 mg/m^2 per os every other day, either from induction or first relapse

Table 6.1: Chemotherapeutic protocol for management of canine lymphoma using epirubicin.

Induction	
Vincristine sulphate	0.5 mg/m^2 intravenously weekly for eight weeks
Prednisolone	40 mg/m^2 per os for 7 days, then 20 mg/m^2 every other day
Cyclophosphamide	50 mg/m^2 per os every other day
Maintenance	
Vincristine sulphate	0.5 mg/m^2 intravenously fortnightly for 34 weeks, then 4 weekly thereafter
Prednisolone	20 mg/m^2 per os every second day for the week subsequent to vincristine treatment
Cyclophosphamide	50 mg/m^2 per os every second day for the week subsequent to vincristine treatment

Table 6.2: Chemotherapeutic protocol for management of canine lymphoma with vincristine, cyclophosphamide and prednisolone.

L-asparginase	400 i.u./kg intramuscularly once or twice, 14 days apart
Doxorubicin	30 mg/m^2 by intravenous infusion every 21 days
Chlorambucil	2 mg/m^2 per os, daily for 7 days then every other day

Table 6.3: Dosages of cytotoxic agents used outwith the standard protocols.

It is recognised that there is variation in survival times as a result of clinician and owner factors, and several clinicians were involved in the treatment of this group of patients. Thus the findings of this part of the study must be interpreted with some degree of caution as to their significance, as the cases lack standardisation. Also, the survival time ranges are large within the individual groups and the mean values may be unrepresentative due to small sample size.

Survival data

Survival times (calculated as time from initiation of chemotherapy to time of death) were available for 55 of the 84 dogs. Fourteen dogs were not treated, either because of the severity of their clinical signs or at the request of the owner. Six of the patients were still alive at time of writing. In nine cases, no survival data was available: these animals had returned for maintenance chemotherapy to the referring veterinary surgeons, who were unable to specify times of euthanasia.

In 56 cases, the ultimate cause of death was known to be the untreated primary disease or relapse of the primary disease. This includes one patient which was inappropriately managed due to histological misdiagnosis and died prematurely of lymphoma. These animals were euthanased, with the exception of two who are recorded to have died at home. In eight cases, the ultimate cause of death was unknown, but recurrence of lymphoma is the most likely cause of death.

Seven dogs died of complications of chemotherapy: five of these animals died of overwhelming sepsis in the face of neutropaenia after drug administration (these cases all had bone marrow involvement, and varying cytopaenias with leukaemic blood pictures). Three of these five dogs had been treated with the anthracycline antibiotic epirubicin (4'-epidoxorubicin) and two with vincristine and cyclophosphamide. The remaining two cases died of cardiac disease, and both of these cases had been treated with epirubicin. However, while one of these dogs had received multiple treatments with epirubicin, the other showed clinical signs of cardiac compromise after only one treatment and was transferred onto the vincristine based protocol. The cardiotoxicity of anthracycline antibiotics is cumulative, and such a rapid development of signs is unusual. It may be that this animal was already suffering from a subclinical cardiomyopathy and that the drug administration either coincided with or was the immediate cause of the animal developing clinical disease. However, both animals had been evaluated for cardiac disease prior to treatment and had been pronounced fit and well. The survival times of these two dogs were above average. The role of this anthracycline in the development of dilated cardiomyopathy is as yet undefined, and both of these animals were of breeds predisposed to this condition (Great Dane and Bull Mastiff). It is possible that epirubicin did not precipitate the development of cardiomyopathy in these cases. The five deaths associated with epirubicin occurred during the initial period of introduction of this drug into hospital protocols and the dose patients received was later reduced.

It is well recognised that anthracycline antibiotics such as doxorubicin are cardiotoxic in the dog (Maudlin and others 1992) but data on epirubicin in the dog is not yet available. However, clinical experience in man has validated the lesser cardiotoxicity of epirubicin compared with other anthracyclines, especially doxorubicin (Muggia and Green 1991).

In seven of the 84 dogs, the immediate cause of death was not lymphoma. Four patients succumbed to other neoplasms. These tumours were a mammary carcinoma with pulmonary metastases, a disseminated haemangiosarcoma, a prostatic adenocarcinoma and an oral fibrosarcoma. Two of these animals were in complete remission of lymphoma at the time of euthanasia, while the third dog had begun induction when investigation of prostatomegaly revealed an adenocarcinoma. The fourth dog had presented due to the presence of a large oral mass and when the diagnosis of concurrent lymphosarcoma was made the owner declined treatment and elected for euthanasia within a few days as the oral mass was interfering severely with the prehension of food. The remainder of the non-lymphoma deaths were comprised of one road traffic accident, one dog which died due to respiratory obstruction by a laryngeal abscess and one which was euthanased due progression of a long-term pre-existing and apparently unrelated neurological condition. The latter dog was in complete remission at the time of death, whereas the other two were in partial remission after a first relapse. These findings are summarised in Table 6.4.

Cause of death	Number of patients
Lymphoma	56
Unknown	8
Drug related toxicity	7
Other unrelated cause	7
Alive at time of writing	6
Total	84

Table 6.4: Causes of death of canine lymphoma patients.

Radiological change and prognosis

It was hoped that this study would help to define the role of radiographic examination in the assessment of prognosis for the individual patient. Excluded

from this part of the study were dogs for whom survival time was unavailable: this automatically excluded the 14 dogs that did not receive chemotherapy. Of the remaining 55 dogs, there were eight dogs who failed to achieve remission and were euthanased or died within 14 days of initiation of chemotherapy, and five dogs for whom survival data was available which died of unrelated causes while being treated for lymphoma. In addition, there was one patient that was treated only with oral prednisolone and cyclophosphamide, reducing expected survival time compared to the other patients, and one patient who was initially inappropriately managed due to histopathological misdiagnosis. This left only 40 cases which had survival data available and had been treated with comparable protocols.

In a rather crude attempt to correlate radiological findings and prognosis, a scoring system was devised in which patients were awarded one point for each radiological abnormality present from the list of parameters which were examined for all patients i.e. suprasternal, cranial mediastinal or tracheobronchial lymphadenopathy, thymic enlargement, pulmonary infiltration, pleural effusion, hepatomegaly, splenomegaly, sublumbar lymphadenopathy, or ascites. No points were given for pleural thickening. No attempt was made to weight the scores as the significance of individual findings is difficult to determine. The mean survival times for the score groups are given below (Table 6.5).

Radiological score	Number of patients	Mean Survival Time (days)	Range of Survival Times (days)
0	4	361	264-464
1	3	220	148-299
2	6	209	35-501
3	12	184	53-852
4	7	194	63-412
5	2	202	129-275
6	5	145	40-407
7	1	27	Not applicable

Table 6.5: Survival times of lymphoma patients relative to radiological findings.

It can be concluded that there is no correlation between the number of radiographic changes observed and the survival time of the individual patient, unless there are no radiological abnormalities. Using regressional analysis to analyse radiographic score and survival time, the radiology score did not correlate significantly with

survival ($p>0.05$, $p=0.053$). (The statistical calculations are given in Appendix 2, page 119). However, the patient numbers are small and a larger group study may find this to be significant, as the effects of the range of survival times within groups would be reduced. Obviously, the small numbers involved in each score group here limit statistical analysis, but it would appear that in general radiology alone is of little value as a prognostic indicator in individual cases of lymphoma. However, the four animals which had no radiological abnormalities detected at time of presentation survived considerably longer than the others and it may be that the absence of radiographic evidence of change is a positive prognostic indicator in cases of multicentric lymphosarcoma. The only animal with a radiology score of 7 had a very short survival time, but it is difficult to assess the significance of this as only a single animal is involved.

Clinical staging and prognosis

The 40 animals which were included in the prognostic investigation above were also assessed relative to the clinical stage of their disease, using the previously described modified W.H.O. staging system (Gorman 1991). The mean survival times for animals with stage III disease compared favourably with those for animals presenting with stage IV or V disease. There was no apparent difference in survival for patients that presented with disease of the same stage with or without systemic signs. Again, the numbers within each group are small, making interpretation of the significance of these findings difficult. However, the difference in survival times between stage III disease and stage IV disease is large and may be significant. In addition, regressional analysis of clinical stage as a prognostic indicator showed that staging correlated significantly with survival ($p<0.05$, $p=0.018$). (The statistical calculations are given in Appendix 2, page 120).

Clinical stage	Number affected	Mean survival time in days (Range)	Overall mean survival time
III(a)	7	302 (35-501)	
III(b)	9	254 (74-852)	275
IV(a)	8	164 (53-413)	
IV(b)	8	181 (70-407)	172
V(a)	1	213	
V(b)	7	102 (27-227)	116

Table 6.6: Clinical stages and survival times for lymphoma series.

It is worth noting that while animals classified as having stage III disease may occasionally have no radiographic abnormalities, radiographic change will be seen in all stage IV cases.

The value of staging as a prognostic indicator has been disputed. However, Squire and others (1973) reported an improved survival time for W.H.O. stage III disease compared to stage IV disease, and Crow (1982) and Carter and others (1987) reported similar improvement for stage III disease compared with stages IV and V, as has been seen in the current study. MacEwen and others (1981) used an alternative but essentially similar scoring system and again demonstrated an improved survival time for animals in the equivalent of stage III disease compared to stage IV or V. In contrast, Cotter (1983) used another modification of the staging system and demonstrated no correlation between stage and survival. In 1987, MacEwen and others carried out a larger retrospective study to evaluate prognostic factors in 147 cases of canine multicentric lymphoma, and, in direct conflict with their previous study, demonstrated no relationship between clinical stage and patient survival. All the animals in the latter study group were in clinical stages III, IV or V. In addition, Postorino and others (1989a) and Hahn and others (1992) found no relationship between clinical stage and survival time. Weller and others (1980) and Crow (1982) reported that dogs which do not show systemic signs [subgroup (a)] have longer survival times than those with systemic signs of disease [subgroup (b)]. The present study fails to confirm this: the subgroup of stage IV animals which showed systemic signs had a slightly longer mean survival time than the subgroup which showed no systemic signs. However, the (b) subgroup of stages III did have slightly shorter mean survival times. The subgroup numbers are too small to be able to attach any real significance to this.

The role of clinical staging as a prognostic indicator for the individual patient is questionable, and the currently used systems are unsatisfactory. The alternative staging systems are all essentially similar in that they subdivide the lymphoma patients based on the distribution of disease within the lymph nodes, the involvement of the liver or spleen and then other organs. Thus the differences between the current staging systems are in the subdivisions of disease extent rather than in fundamental approach. Although a multicentre prospective study may help to ascertain whether clinical stage has any bearing on survival time for the disease as a whole it seems unlikely that this system will be of any value in indicating prognosis for the individual patient, where clinical findings, biochemical and haematological parameters (including bone marrow evaluation) have more relevance.

Hypercalcaemia and prognosis

Serum calcium values were available for 78 of the 84 patients. Eight animals were hypercalcaemic on presentation, after adjustment of relative to serum albumin. Four of the eight patients received no treatment for lymphoma: three of these patients presented in an advanced stage of renal failure which unfortunately proved irreversible on attempted medical management and in the fourth case the owner elected for euthanasia after diagnosis. Although hypercalcaemia can lead to renal damage which is reversible in the first instance it can ultimately result in a severe and irreversible nephropathy (Kruth and Carter 1990).

Of the four animals which were treated, one failed to achieve remission and was euthanased after five days when investigation of prostatomegaly revealed it had a concurrent prostatic adenocarcinoma. This may have been contributing to the refractory hypercalcaemia in this patient.

The longest surviving patient in this group had a survival time of 280 days. This animal was noted to have marked enlargement of the sublumbar lymph nodes, especially the medial iliac node, on initial radiological evaluation. These nodes continued to gradually increase in size while the animal was on chemotherapy and at post mortem the enlarged abdominal nodes were found to be completely replaced by sheets of adenocarcinomatous cells. Although the pattern of this was consistent with origin from the glands of the anal sacs no mass was found at this site. This lesion may have contributed to or been responsible for this animal's hypercalcaemia, which continued to be a problem even when she was in complete remission in terms of lymphoma. The immediate cause of death (euthanasia) in this patient was a metastasised haemangiosarcoma.

The other two treated patients survived for 129 and 178 days on therapy. The clinical stage of both these animals was III, and the average survival time for this group as a whole was 275 days. It is recognised that hypercalcaemic patients have shorter survival times than those lymphoma patients which do not suffer from this paraneoplastic disease (Weller and others 1982b). Unfortunately, as only two of the hypercalcaemic patients in this study group were treated and euthanased due to relapse of lymphoma the significance of the comparative survival times is impossible to assess. However, the rapid demise of the animals within the group which were in irreversible renal failure at time of diagnosis illustrates the negative effects of this paraneoplastic syndrome on prognosis.

Histological classification and prognosis

Histological classification of canine lymphoma has been based largely on the Rappaport system of classification of non-Hodgkin's lymphoma in man. The basis of categorisation has been the architectural pattern (diffuse or nodular) and the cell type (poorly or well differentiated lymphocytic, histiocytic or undifferentiated cells). These descriptions do not take into account the immunological or functional characteristics of the cells. This system is a useful in the determination of treatment regimes in man, and is a reliable prognostic indicator (Arseneau and Rosenthal 1980) but unfortunately appears to be of no value as a predictor of response to therapy or survival for individual dogs (Squire and others 1973, Weller and others 1980).

In humans, an additional system has been developed which also takes into account the mitotic index of the tumour, tissue architecture and cell classification based on nuclear and nucleolar morphology rather than morphological nomenclature. This has been modified for use in canine tumours but is limited by the narrower range of variation in canine tumours (most have diffuse architecture and are of intermediate or high grade) (MacEwen and Young 1989, Wellman 1993). In addition, the immunological classification of the tumour cell may have prognostic relevance, and certain cell surface markers are associated with variations in response to chemotherapy (MacEwen and Young 1989). Unfortunately, the histologic appearance of malignant lymphoid cells does not appear to be associated with the presence of B or T cell markers in either the dog or man (Holmberg and others 1977).

CHAPTER 7.

CONCLUSIONS

CONCLUSIONS

The aims of the work presented in this study were:

1. to identify the radiographic features of a large number of cases of canine multicentric lymphoma, and to document the frequency with which individual abnormalities or combinations of abnormalities occurred
2. to assess the role of radiographic examination in the diagnosis of this disease, and to identify the specific problems encountered in interpretation of the radiographs of these patients
3. to analyse the relationship between the thoracic radiological findings and the occurrence of hypercalcaemia
4. to investigate the prognostic significance of the radiological findings

The radiological findings in multicentric lymphoma

It was concluded from this study that multicentric lymphoma is not a radiological diagnosis i.e. that a diagnosis of this disease cannot be made on the basis of radiographic findings alone. A proportion of animals (very approximately 20%) will show no radiographic abnormalities on either thoracic or abdominal radiographs, or both.

The most commonly identified thoracic radiographic abnormality is suprasternal lymphadenopathy, and this is usually seen in association with enlargement of the cranial mediastinal or tracheobronchial nodes. Thoracic lymphadenopathy and pulmonary infiltration are seen more frequently than thymic enlargement or pleural effusion. It is more common to see two or three concurrent abnormalities than to identify a solitary change.

Thymic enlargement is a relatively infrequent occurrence in multicentric lymphoma, as is pleural effusion. The presence of pleural fluid is a major obstacle to radiological evaluation of the cranial mediastinal structures and assessment of pulmonary patterns, which might otherwise alert the radiologist to the possible diagnosis of lymphoma.

The abdominal abnormalities most commonly associated with lymphoma are hepatomegaly, splenomegaly and sublumbar lymphadenopathy. These changes are frequently seen in combination, in some way compensating for the non-specific nature of the individual findings. Ascites is seen less frequently, and may vary

from a very small volume of fluid, mimicking localised peritonitis or carcinomatosis, to a very large volume of fluid that obscures the abdominal organs. Again, this makes assessment of the other abnormalities associated with lymphoma difficult.

Radiographic interpretation and its role

Radiologically, lymphoma presents the interpreter with a number of challenges. In technical terms, one of the main problems identified was inadequate pulling forward of the forelimbs on thoracic radiographs. This made assessment of the suprasternal nodes difficult, and was a common reason for exclusion of films from the trial group.

The changes associated with slight enlargement of the tracheobronchial lymph nodes are often subtle and may be overlooked. However, concurrent enlargement of these nodes is commonly seen in patients with pulmonary infiltration, and this finding greatly increases the index of suspicion of lymphoma. The patterns of pulmonary disease seen in lymphoma vary from subtle interstitial change to strikingly mixed patterns, and can be difficult to define or differentiate from senescent change or disease of other cause.

Although pulmonary change may appear in several forms, the most commonly encountered patterns of pulmonary disease are disseminated miliary nodular or reticulonodular patterns. Occasionally, alveolar markings may be seen in association with disseminated interstitial disease. The significance of the prominent peribronchial shadows seen in many of the animals with interstitial change is difficult to assess, but may represent peribronchial lymphoid infiltration. There are many differential diagnoses for the various pulmonary patterns seen in lymphoma, and although the classically described reticulonodular appearance is fairly distinctive if marked, similar change can result from other less common conditions.

Hepatomegaly and splenomegaly are both assessed subjectively, and are thus prone to interpreter error. Hepatomegaly is associated with many conditions, and the appearance of an enlarged liver may result artefactually from patient and technical factors. Splenomegaly may also occur due to many causes, including extramedullary haemopoiesis or as a result of blood pooling in animals sedated with phenothiazine tranquillisers or anaesthetised with barbiturates. Although sublumbar lymphadenopathy is readily identifiable, enlargement of the mesenteric nodes is difficult to identify on plain films and may be under diagnosed.

Where there is pleural or peritoneal effusion, it can be difficult to identify other structures which may be involved in the disease process and suspicion of lymphoma may not be aroused. In these situations, other techniques including ultrasonographic examination and cytological evaluation of the abnormal fluid are more helpful diagnostically than radiographic examination.

As lymphoma is not a radiological diagnosis, the role of radiology in the assessment in these patients may be questioned. However, although the individual abnormalities seen are of variable specificity, when several of these are seen together then the radiological findings are highly suggestive of lymphoma, especially in the United Kingdom, where systemic fungal disease is rare. Additionally, radiographic examination is vital if the animals are to be accurately clinically staged, as it allows assessment of the extent of internal disease. Radiology also provides information which may be pertinent to the selection of chemotherapeutic protocols for individual patients by alerting the clinician to the presence of concurrent disease which has a bearing on treatment and prognosis.

Hypercalcaemia and thoracic radiological abnormalities

The relationship between cranial mediastinal disease and hypercalcaemia is unclear. The findings of this study suggest that cranial mediastinal disease is neither a prerequisite for nor a disproportionately common finding in hypercalcaemia. However, there may be a relationship between lymphoma of thymic origin and hypercalcaemia. It is suggested that a prospective multicentre study which assessed this relationship in a large number of patients may clarify the situation. This would require typing of tumours with mediastinal involvement into T-cell and B-cell groups, and accurate division of cases into those of B-cell origin with thymic or cranial mediastinal node involvement from tumours of thymic origin with multicentric involvement.

The prognostic significance of the radiological findings

In general, radiology alone would appear to have no place as a prognostic indicator for the individual patient. However, the absence of radiological abnormalities may be a positive prognostic indicator. Statistically, the relationship between the radiological findings and survival time was insignificant. However, the relationship between the clinical stage of disease and survival was significant, and radiology is a vital part of the staging process. Additionally, it appeared that animals with stage

III disease had considerably longer mean survival times than those with more advanced disease. Animals with stage III disease may in some cases have no radiological abnormalities, whereas those with stage IV disease will always have radiological changes. However, the large range in survival times within the small groups of animals with the same clinical stage of disease would suggest that these generalisations are of little value to the individual patient.

APPENDICES

APPENDIX 1: PATIENT RESULTS

The recorded thoracic and abdominal radiographic abnormalities are presented in Appendices 1.a (pages 107-110) and 1.b (pages 111-113) respectively. The clinical stages, survival times and adjusted serum calcium values are given in Appendix 1.c (pages 114-117).

The abbreviations used in the tables are:

Breed	KCCS	King Charles Cavalier Spaniel
	WHWT	West Highland White Terrier
Sex	M	Male, entire
	C	Male, castrated
	F	Female, entire
	S	Female, spayed
Calcium units	mmol/l	millimoles per litre

Ages are given in years.

Number	Breed	Age	Sex	Suprasternal lymphadeno-pathy	Detrimental forelimb positioning	Suprasternal lymph node score	Cranial mediastinal lymph node enlargement	Tracheobronchial lymph node enlargement	Tracheo-bronchial node score	Thymic enlargement	Abnormal pulmonary density	Pleural change
103020	Doberman Pinscher	2.0	S	Yes	Yes	1	Yes	No	0	No	No	No
104259	Boxer	5.0	F	Yes	No	2	Yes	Yes	1	Yes	Yes	No
108386	Cross	9.7	S	Yes	No	1	No	No	0	No	No	No
108548	Cross	4.5	F	Yes	No	1	No	No	0	No	Yes	Yes
108556	German Shepherd Dog	2.0	F	Yes	No	3	Yes	Yes	1	No	Yes	Yes
109341	Great Dane	5.0	F	No	No	0	No	No	0	No	Yes	No
109342	Irish Setter	9.0	M	No	No	0	No	No	0	No	No	No
109400	Doberman Pinscher	8.0	M	No	No	0	No	No	0	No	No	No
109456	Cross	9.0	M	Yes	No	1	Yes	Yes	1	No	Yes	Yes
109969	Labrador	10.0	S	No	No	0	No	No	0	No	No	Yes
111055	Scottish Terrier	9.0	M	No	Yes	0	No	No	0	No	No	No
111187	Irish Setter	13.0	M	Yes	No	1	No	No	0	No	Yes	No
111369	Greyhound	6.0	M	No	No	0	No	Yes	1	No	Yes	No
111961	Retriever	5.0	F	Yes	Yes	2	No	Yes	1	No	No	No
111979	KCCS	5.0	F	No	No	0	No	Yes	1	No	No	Yes
112614	Airedale	6.0	F	Yes	No	1	Yes	Yes	2	No	Yes	No
112955	Irish Setter	4.0	S	Yes	No	2	No	No	0	No	No	No
113069	German Shepherd Dog	7.0	M	No	No	0	No	No	0	No	No	No
113168	Cross	11.0	M	No	No	0	No	No	0	No	No	No
113915	Miniature Poodle	4.0	M	No	No	0	No	No	0	No	Yes	No
114189	Bull Mastiff	4.5	S	No	No	0	No	No	0	No	No	No
114195	Cross	8.0	M	No	No	0	No	No	0	No	No	Yes
114328	Corgi	8.0	M	No	No	0	No	No	0	No	Yes	No
114768	Retriever	3.5	M	No	No	0	No	No	0	No	No	No
114800	Old English Sheepdog	10.0	S	Yes	Yes	1	No	No	0	No	Yes	No
114887	English Springer Spaniel	4.0	M	No	No	0	No	No	0	No	No	Yes

Number	Breed	Age	Sex	Suprasternal lymphadeno-pathy	Detrimental forelimb positioning	Suprasternal lymph node score	Cranial mediastinal lymph node enlargement	Tracheobronchial lymph node enlargement	Tracheo-bronchial node score	Thymic enlargement	Abnormal pulmonary density	Pleural change
114891	Great Dane	7.0	M	Yes	No	1	No	No	0	No	No	No
115029	Labrador	8.0	C	No	No	0	No	No	0	No	No	No
115030	Labrador	8.0	M	No	Yes	0	Yes	No	0	Yes	Yes	No
115069	Irish Setter	5.0	F	Yes	No	2	Yes	No	0	No	Yes	No
115074	Old English Sheepdog	7.0	M	No	No	0	No	Yes	1	No	Yes	No
115251	Cross	9.5	M	Yes	No	1	No	No	0	No	Yes	No
115448	Shetland Sheepdog	4.0	F	No	No	0	No	No	0	No	Yes	No
115498	Border Collie	5.0	M	No	Yes	0	No	No	0	No	No	No
115616	Cross	4.0	M	No	No	0	No	No	0	No	Yes	No
115824	Lhaso Apso	4.0	M	No	No	0	No	No	0	No	No	No
115827	Cross	5.5	M	No	Yes	0	Yes	Yes	2	No	No	No
115839	Bull Mastiff	6.5	F	No	No	0	No	Yes	2	No	Yes	Yes
116190	Rottweiller	2.0	S	No	No	0	No	No	0	No	No	No
116202	Labrador	5.0	M	No	Yes	0	Yes	Yes	2	No	Yes	Yes
116350	German Shepherd Dog	6.0	M	Yes	Yes	1	No	No	0	No	No	No
116501	Jack Russell Terrier	5.0	F	No	Yes	0	No	No	0	No	No	Yes
116577	Labrador	11.0	M	No	No	0	Yes	No	0	Yes	Yes	No
116793	Bull Mastiff	10.0	S	Yes	No	1	No	No	0	No	No	No
116869	Cross	4.5	S	No	Yes	0	No	Yes	1	No	Yes	No
117127	Cross	8.0	M	No	Yes	0	Yes	No	0	No	Yes	Yes
117240	Cross	11.5	F	No	No	0	No	No	0	No	No	Yes
117455	Labrador	10.0	F	No	No	0	Yes	Yes	1	No	No	No
117986	Tibetan Terrier	3.0	M	No	No	0	No	No	0	No	Yes	Yes
118031	WHWT	11.0	M	Yes	Yes	2	Yes	Yes	3	No	No	No
118039	Cross	13.0	S	No	No	0	No	No	0	No	No	No
118326	Cross	6.0	S	Yes	No	2	No	Yes	1	No	Yes	No

Number	Breed	Age	Sex	Suprasternal lymphadeno-pathy	Detrimental forelimb positioning	Suprasternal lymph node score	Cranial mediastinal lymph node enlargement	Tracheobronchial lymph node enlargement	Tracheo-bronchial node score	Thymic enlargement	Abnormal pulmonary density	Pleural change
118641	Labrador	6.0	M	No	No	0	No	No	0	No	Yes	No
118642	German Shepherd Dog	7.0	S	Yes	Yes	1	No	No	0	No	No	No
118650	Boxer	9.0	M	Yes	Yes	1	Yes	No	0	No	No	No
118916	Labrador	7.7	F	No	Yes	0	No	Yes	1	No	No	No
118919	Retriever	5.0	M	Yes	No	2	Yes	Yes	1	Yes	No	No
118979	Cross	4.5	S	Yes	No	3	No	No	0	No	No	Yes
119024	Labrador	9.0	M	Yes	Yes	1	No	Yes	2	No	Yes	Yes
119125	Border Collie	5.5	F	Yes	Yes	2	Yes	Yes	3	No	No	No
119391	Gordon Setter	9.0	M	Yes	No	2	Yes	No	0	Yes	No	No
119595	Labrador	9.9	F	No	No	0	Yes	Yes	2	No	Yes	No
119654	Cross	6.0	F	No	Yes	0	No	No	0	No	No	No
119693	KCCS	7.0	F	Yes	Yes	2	Yes	Yes	1	No	No	No
119836	Labrador	2.8	M	No	Yes	0	No	No	0	No	No	No
119984	German Shepherd Dog	4.5	C	Yes	Yes	1	No	Yes	1	No	No	No
120188	Boxer	6.5	M	Yes	Yes	2	Yes	Yes	1	No	Yes	No
120261	Airedale	2.0	F	No	Yes	0	No	No	0	No	No	No
120264	Cross	16.5	S	Yes	No	1	No	Yes	2	No	No	No
120294	Retriever	10.0	S	Yes	No	2	Yes	Yes	3	No	No	No
120337	Labrador	10.0	S	No	No	0	No	No	0	No	No	Yes
120362	Cross	10.0	F	Yes	No	1	Yes	Yes	2	No	Yes	Yes
120384	Retriever	11.4	F	No	No	0	No	No	0	No	No	No
120591	Retriever	7.0	F	No	No	0	No	No	0	No	No	No
120907	Labrador	10.0	M	Yes	Yes	1	No	Yes	1	No	No	No
120910	WHWT	3.7	S	Yes	No	1	No	No	0	No	No	No
121061	Rough Collie	5.0	M	No	No	0	No	No	0	No	No	No
121093	German Shepherd Dog	6.0	S	No	Yes	0	No	No	0	No	Yes	No
121139	Beagle	9.7	M	No	Yes	0	No	No	0	No	No	No

Number	Breed	Age	Sex	Suprasternal lymphadeno-pathy	Detrimental forelimb positioning	Suprasternal lymph node score	Cranial mediastinal lymph node enlargement	Tracheobronchial lymph node enlargement	Tracheo-bronchial node score	Thymic enlargement	Abnormal pulmonary density	Pleural change
121343	Boxer	2.6	F	Yes	No	1	No	Yes	2	No	No	No
121396	Rottweiller	6.0	F	No	No	0	No	No	0	No	Yes	Yes
121605	Boxer	8.0	F	No	Yes	0	No	No	0	Yes	No	No
121743	Rottweiller	8.0	M	No	No	0	No	No	0	No	No	No
121861	Cross	7.0	M	No	No	0	No	No	0	No	No	Yes

Number	Breed	Age	Sex	Hepatomegaly	Splenomegaly	Sublumbar lymph node enlargement	Sublumbar lymph node score	Ascites
103020	Doberman Pinscher	2.00	S	No	No	Yes	1	No
104259	Boxer	5.00	F	No	No	Yes	1	No
108386	Cross	9.70	S	No	No	No	0	No
108548	Cross	4.50	F	Yes	No	No	0	No
108556	German Shepherd Dog	2.00	F	Yes	No	No	0	No
109341	Great Dane	5.00	F	No	Yes	No	0	Yes
109342	Irish Setter	9.00	M	Yes	Yes	Yes	2	No
109400	Doberman Pinscher	8.00	M	Yes	Yes	Yes	1	No
109456	Cross	9.00	M	Yes	Yes	Yes	2	No
109969	Labrador	10.00	S	No	No	Yes	1	No
111055	Scottish Terrier	9.00	M	Yes	Yes	Yes	1	No
111369	Greyhound	6.00	M	No	Yes	Yes	2	Yes
111961	Retriever	5.00	F	No	No	Yes	3	No
111979	KCCS	5.00	F	Yes	No	Yes	2	No
112614	Airedale	6.00	F	No	Yes	Yes	2	No
112955	Irish Setter	4.00	S	No	Yes	Yes	2	No
113168	Cross	11.00	M	Yes	Yes	Yes	2	No
113915	Miniature Poodle	4.00	M	No	No	Yes	2	No
114189	Bull Mastiff	4.50	S	No	No	No	0	No
114195	Cross	8.00	M	Yes	Yes	Yes	3	No
114328	Corgi	8.00	M	No	No	Yes	1	No
114768	Retriever	3.50	M	No	No	No	0	No
114800	Old English Sheepdog	10.00	S	No	No	Yes	2	No
114891	Great Dane	7.00	M	No	No	Yes	3	No
115030	Labrador	8.00	M	Yes	Yes	Yes	2	No
115069	Irish Setter	5.00	F	Yes	No	Yes	3	No

Number	Breed	Age	Sex	Hepatomegaly	Splenomegaly	Sublumbar lymph node enlargement	Sublumbar lymph node score	Ascites
115074	Old English Sheepdog	7.00	M	Yes	Yes	Yes	2	Yes
115251	Cross	9.50	M	No	Yes	Yes	2	No
115448	Shetland Sheepdog	4.00	F	No	No	No	0	No
115498	Border Collie	5.00	M	No	No	No	0	No
115616	Cross	4.00	M	No	No	Yes	2	No
115824	Lhaso Apso	4.00	M	Yes	Yes	No	0	No
115827	Cross	5.50	M	Yes	No	Yes	2	No
115839	Bull Mastiff	6.50	F	No	Yes	Yes	2	No
116190	Rottweiller	2.00	S	Yes	Yes	No	0	No
116202	Labrador	5.00	M	Yes	No	Yes	3	Yes
116350	German Shepherd Dog	6.00	M	No	No	Yes	1	No
116501	Jack Russell Terrier	5.00	F	Yes	No	Yes	1	No
116793	Bull Mastiff	10.00	S	No	No	Yes	2	Yes
116869	Cross	4.50	S	No	No	Yes	2	No
117127	Cross	8.00	M	Yes	Yes	Yes	2	No
117240	Cross	11.50	F	No	No	Yes	2	Yes
117455	Labrador	10.00	F	Yes	Yes	Yes	2	No
117986	Tibetan Terrier	3.00	M	Yes	No	Yes	2	No
118031	WHWT	11.00	M	Yes	Yes	Yes	3	No
118039	Cross	13.00	S	Yes	Yes	Yes	1	No
118326	Cross	6.00	S	No	Yes	Yes	3	No
118641	Labrador	6.00	M	Yes	Yes	No	0	No
118642	German Shepherd Dog	7.00	S	Yes	Yes	Yes	3	No
118650	Boxer	9.00	M	No	Yes	Yes	2	No
118916	Labrador	7.70	F	No	Yes	Yes	3	No
118919	Retriever	5.00	M	No	No	Yes	1	No

Number	Breed	Age	Sex	Hepatomegaly	Splenomegaly	Sublumbar lymph node enlargement	Sublumbar lymph node score	Ascites
118979	Cross	4.50	S	Yes	Yes	Yes	2	Yes
119024	Labrador	9.00	M	Yes	Yes	Yes	3	No
119125	Border Collie	5.50	F	Yes	Yes	Yes	3	No
119391	Gordon Setter	9.00	M	Yes	No	Yes	2	No
119595	Labrador	9.90	F	Yes	Yes	Yes	3	No
119654	Cross	6.00	F	Yes	No	No	0	No
119693	KCCS	7.00	F	Yes	No	Yes	3	No
119836	Labrador	2.80	M	No	No	No	0	Yes
119984	German Shepherd Dog	4.50	C	Yes	Yes	Yes	3	No
120188	Boxer	6.50	M	No	No	No	0	No
120261	Airedale	2.00	F	No	Yes	Yes	1	No
120264	Cross	16.50	S	Yes	No	Yes	3	No
120294	Retriever	10.00	S	No	No	Yes	2	No
120337	Labrador	10.00	S	Yes	Yes	Yes	2	Yes
120362	Cross	10.00	F	Yes	Yes	Yes	2	No
120384	Retriever	11.40	F	Yes	No	No	0	No
120591	Retriever	7.00	F	Yes	No	No	0	No
120907	Labrador	10.00	M	Yes	No	Yes	3	No
120910	WHWT	3.70	S	No	No	Yes	1	No
121061	Rough Collie	5.00	M	No	No	No	0	No
121093	German Shepherd Dog	6.00	S	Yes	Yes	Yes	3	No
121139	Beagle	9.67	M	Yes	Yes	Yes	1	No
121343	Boxer	2.60	S	No	No	Yes	2	No
121396	Rottweiller	6.00	F	Yes	No	Yes	2	No
121605	Boxer	8.00	F	No	No	No	0	No
121743	Rottweiller	8.00	M	Yes	Yes	No	0	Yes
121861	Cross	7.00	M	No	No	No	0	No

Number	Breed	Age	Sex	Clinical stage	Survival (days)	Adjusted serum calcium (mmol/l)
103020	Doberman Pinscher	2.0	S	III (a)	Not available	Not available
104259	Boxer	5.0	F	V(b)	Not available	Not available
108386	Cross	9.7	S	III(b)	299	2.78
108548	Cross	4.5	F	V(b)	227	2.61
108556	German Shepherd Dog	2.0	F	V(b)	No treatment given	2.59
109341	Great Dane	5.0	F	IV(a)	67	2.96
109342	Irish Setter	9.0	M	IV(b)	113	2.59
109400	Doberman Pinscher	8.0	M	IV(b)	108	2.69
109456	Cross	9.0	M	V(b)	27	2.42
109969	Labrador	10.0	S	III(a)	377	2.54
111055	Scottish Terrier	9.0	M	IV(a)	53	2.42
111187	Irish Setter	13.0	M	V(b)	Not available	Not available
111369	Greyhound	6.0	M	IV(b)	8	1.59
111961	Retriever	5.0	F	III(b)	74	2.62
111979	KCCS	5.0	F	V(b)	No treatment given	2.61
112614	Airedale	6.0	F	IV(a)	114	2.7
112955	Irish Setter	4.0	S	IV(a)	126	2.24
113069	German Shepherd Dog	7.0	M	III(a)	464	2.65
113168	Cross	11.0	M	IV(a)	167	2.24
113915	Miniature Poodle	4.0	M	V(a)	Not available	Not available
114189	Bull Mastiff	4.5	S	III(a)	264	2.95
114195	Cross	8.0	M	V(b)	8	2.76
114328	Corgi	8.0	M	V(a)	Not available	Not available
114768	Retriever	3.5	M	V(b)	No treatment given	**3.92**
114800	Old English Sheepdog	10.0	S	III(b)	852	2.74
114887	English Springer Spaniel	4.0	M	V(b)	148	2.65
114891	Great Dane	7.0	M	V(b)	No treatment given	**3.96**
115029	Labrador	8.0	C	III(b)	304	2.6

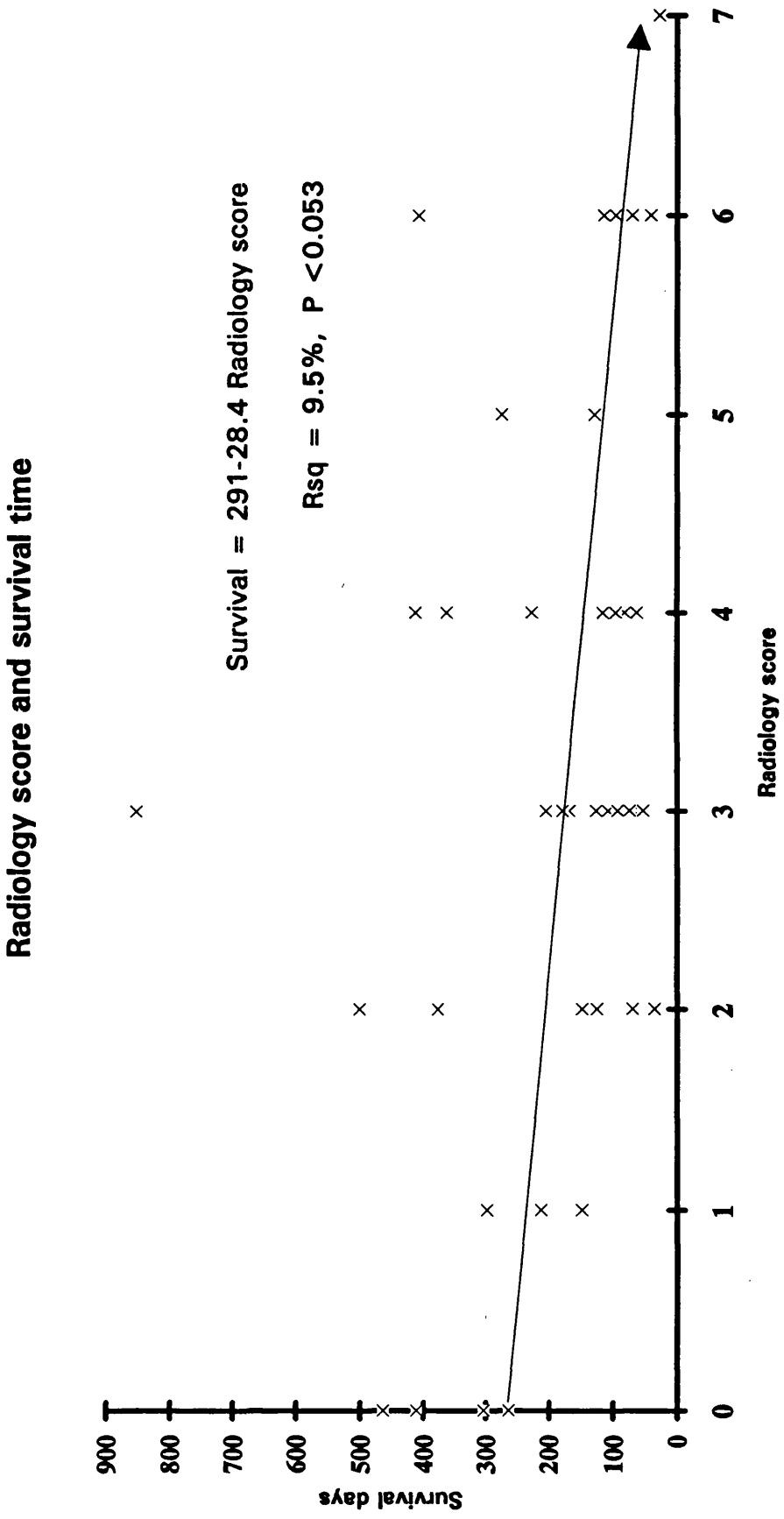
Number	Breed	Age	Sex	Clinical stage	Survival (days)	Adjusted serum calcium (mmol/l)
115030	Labrador	8.0	M	V(b)	No treatment given	2.56
115069	Irish Setter	5.0	F	IV(a)	258	2.32
115074	Old English Sheepdog	7.0	M	V(b)	9	2.68
115251	Cross	9.5	M	V(b)	No treatment given	2.19
115448	Shetland Sheepdog	4.0	F	III(b)	No treatment given	2.71
115498	Border Collie	5.0	M	III(a)	412	2.42
115616	Cross	4.0	M	III(a)	501	2.59
115824	Lhaso Apso	4.0	M	IV(b)	125	2.76
115827	Cross	5.5	M	IV(a)	413	2.55
115839	Bull Mastiff	6.5	F	IV(b)	362	2.64
116190	Rottweiller	2.0	S	V(b)	No treatment given	2.56
116202	Labrador	5.0	M	IV(b)	12	2.67
116350	German Shepherd Dog	6.0	M	III(a)	35	2.99
116501	Jack Russell Terrier	5.0	F	V(b)	No treatment given	2.27
116577	Labrador	11.0	M	IV(b)	14	2.45
116793	Bull Mastiff	10.0	S	IV(b)	43	2.54
116869	Cross	4.5	S	III(b)	205	2.55
117127	Cross	8.0	M	V(b)	4	2.68
117240	Cross	11.5	F	III(b)	148	2.61
117455	Labrador	10.0	F	IV(b)	4	2.56
117986	Tibetan Terrier	3.0	M	V(b)	No treatment given	2.7
118031	WHWT	11.0	M	IV(b)	407	2.46
118039	Cross	13.0	S	IV(b)	168	2.47
118326	Cross	6.0	S	IV(a)	275	2.72

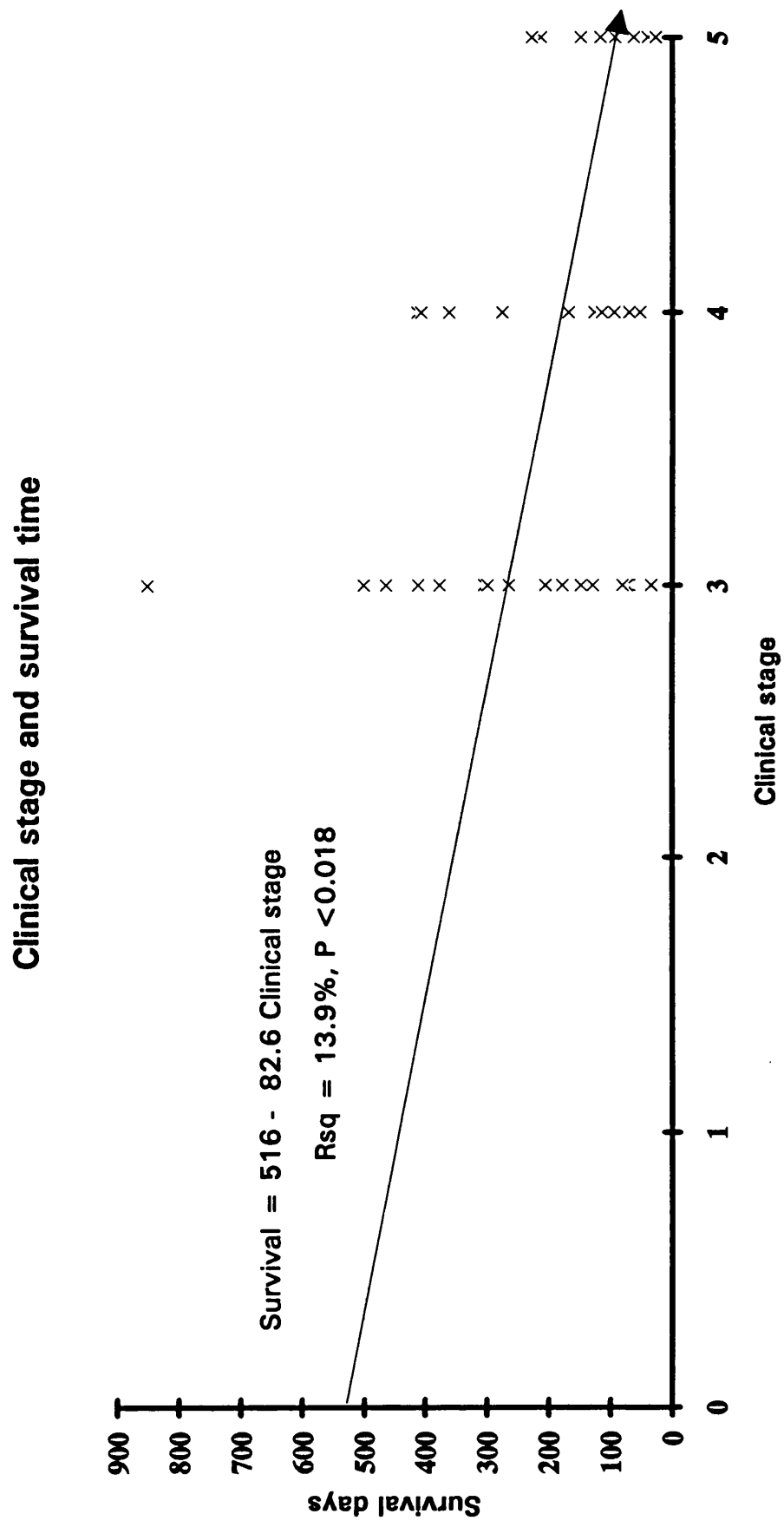
Number	Breed	Age	Sex	Clinical stage	Survival (days)	Adjusted serum calcium (mmol/l)
118641	Labrador	6.0	M	V(b)	93	2.62
118642	German Shepherd Dog	7.0	S	IV(a)	Not available	2.63
118650	Boxer	9.0	M	IV(a)	95	2.78
118916	Labrador	7.7	F	IV(b)	280	**4.57**
118919	Retriever	5.0	M	III(b)	129	**4.7**
118979	Cross	4.5	S	V(b)	40	2.47
119024	Labrador	9.0	M	IV(b)	Not available	2.53
119125	Border Collie	5.5	F	IV(b)	95	2.6
119391	Gordon Setter	9.0	M	V(b)	No treatment given	2.72
119595	Labrador	9.9	F	IV(b)	70	2.43
119654	Cross	6.0	F	IV(b)	67	2.62
119693	KCCS	7.0	F	IV(b)	132	2.8
119836	Labrador	2.8	M	II(b)	Not available	2.69
119984	German Shepherd Dog	4.5	C	IV(a)	Not available	2.57
120188	Boxer	6.5	M	V(b)	116	3
120261	Airedale	2.0	F	III(a)	Alive at time of writing	2.95
120264	Cross	16.5	S	IV(b)	No treatment given	Sample lipaemic
120294	Retriever	10.0	S	III(b)	81	2.73
120337	Labrador	10.0	S	V(b)	63	2.88
120362	Cross	10.0	F	IV(a)	Alive at time of writing	2.75
120384	Retriever	11.4	F	V(b)	No treatment given	**3.94**
120591	Retriever	7.0	F	V(a)	213	2.8
120907	Labrador	10.0	M	IV(a)	77	2.59
120910	WHWT	3.7	S	III(a)	70	2.69
121061	Rough Collie	5.0	M	II(b)	5	**4.1**
121093	German Shepherd Dog	6.0	S	IV(a)	Alive at time of writing	2.7
121139	Beagle	9.7	M	IV(a)	Alive at time of writing	2.73

Number	Breed	Age	Sex	Clinical stage	Survival (days)	Adjusted serum calcium (mmol/l)
121343	Boxer	2.6	F	III(b)	178	**3.72**
121396	Rottweiller	6.0	F	IV(a)	Alive at time of writing	2.77
121605	Boxer	8.0	F	V(b)	No treatment given	**3.65**
121743	Rottweiller	8.0	M	IV(b)	4	2.9
121861	Cross	7.0	M	III(a)	Alive at time of writing	2.75

APPENDIX 2: STATISTICAL ANALYSES

The statistical analyses of radiology score and clinical stage were carried out as previosly described, using *Excel 4.0* (Microsoft) and *Minitab 8.0* (Minitab Inc). The graphs generated are shown on pages 119 and 120.


Radiology score and survival time
Survival = 291-28.4 Radiology score
Rsq = 9.5%, P <0.053
Survival days
900
800
700
600
500
400
300
200
100
0
0
1
2
3
4
5
6
7
Radiology score


Clinical stage and survival time
Survival = 516 - 82.6 Clinical stage
Rsq = 13.9%, P <0.018
Survival days
900
800
700
600
500
400
300
200
100
0
0
1
2
3
4
5
Clinical stage

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