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Conformity and controversies in the diagnosis, staging and follow-up evaluation of canine nodal lymphoma: a systematic review of the last 15 years of published literature

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Abstract

Diagnostic methods used in the initial and post-treatment evaluation of canine lymphoma are heterogeneous and can vary within countries and institutions. Accurate reporting of clinical stage and response assessment is crucial in determining the treatment efficacy and predicting prognosis. This study comprises a systematic review of all available canine multicentric lymphoma studies published over a period of 15 years. Data concerning clinical stage evaluation and response assessment procedures were extracted and compared. Sixty-five studies met the eligibility criteria. The survey results expose variations in diagnostic criteria and treatment response assessment in canine multicentric lymphoma. Variations in staging procedures performed and recorded led to an unquantifiable heterogeneity among patients in and between studies, making it difficult to compare treatment efficacies. Awareness of this inconsistency of procedure and reporting may help in the design of future clinical trials.

Introduction

Variation in diagnostic criteria and inconsistencies in staging procedures in veterinary cancer patients have important consequences for patient selection in clinical studies and will often preclude meaningful comparison of published data between studies. Standardizing staging and treatment response assessment criteria are therefore critical to the successful performance of clinical trials and to subsequent evaluations and comparisons of study outcomes.

Canine lymphoma is a heterogeneous group of diseases that exhibit distinct biological behaviors according to histological subtype and extent of systemic distribution.[1,2] In addition to histopathological classification, clinical stage is one of the most important prognostic factors and may therefore represent a key variable in dictating treatment with respect to drug choice. Indeed, modern methods for diagnosis and staging of human lymphoma have improved in parallel with the spectrum of therapeutic options in recent years.[3]

Modern lymphoma classifications are based on the rationale of defining clinico-pathological disease entities, enabling greater insight into the biological mechanisms that underlie specific diseases and the clinical consequences in terms of progression patterns and responses to different treatments.[4,5] The ultimate goal is to develop treatment protocols that are specifically tailored to the characteristics of the individual disease entity.[6]

Much emphasis has lately been placed on the morphological subtype of disease.[1,4,7] Whereas morphological subtype is not expected to change in response to therapy, for accurate evaluation of treatment response, a complete knowledge of lymphoma extension prior to therapy makes it possible to

accurately re-stage dogs at the end of therapy and thus to define the quality of response. Standardized methods for staging are essential to make critical assessments and comparisons between different therapeutic strategies; incomplete or inconsistent staging work-up impedes comparison of study results.

Currently, controversies exist regarding the extent of staging work-up that needs to be carried out at initial presentation and after completion of chemotherapy to assess treatment response. Over the years, much of this controversy arose from the assumption that an extensive staging work-up, while it might result in stage migration, did not influence prognosis or therapy.[8]

Recent progress in the field of canine lymphoma is not limited to improvements in determining morphological subtype. Refinements have also been made in molecular diagnosis and detection of minimal residual disease (MRD). A prognostic impact of the presence of MRD as detected by thymidine kinase assay[9] or PARR (PCR for Antigen Receptor Rearrangement) testing[10] has been demonstrated. While progress has been made in the publication of consensus guidelines concerning the standardization of lymph node assessment by physical examination (VCOG, Veterinary Cooperative Oncology Group), in the light of such recent progress, it can now be considered very likely that these guidelines would tend to overstate complete remission rates and understate progression rates.[11]

In order to continue the current trajectory of progress in our understanding and management of canine lymphoma, and to be able to retrospectively evaluate and compare between clinical studies, it is clear that there is a need for greater

accuracy in the staging of lymphoma at first presentation and the assessment of treatment response.

In this systematic review, data that report various staging methods in canine lymphoma are summarized. The main aim was to determine to what extent different approaches to evaluate treatment efficacy were comparable. In conclusion, we will make some recommendations for further studies that may help address significant unresolved clinical issues surrounding the disease.

Methods

Literature search and study selection processes

A literature search limited to manuscripts published from January 1999 to December 2014 was performed. The search was limited to a 15 year period to ensure the studies represented contemporary diagnostic procedures and management options.

A systematic MEDLINE search of articles was conducted by using the following search terms: “lymphoma” AND “dog” OR “canine” AND “treatment” OR “therapy” OR “chemotherapy” OR “immunotherapy” OR “adoptive therapy” AND “prognosis” OR “outcome” OR “assessment” OR “survival” OR “progression” OR “remission” OR “relapse” OR “disease-free”. The following were inclusion criteria for the studies to be selected: the article was published in English; the full text was available for review; the number of cases was more than 5; and finally the study was published in a peer-reviewed journal. Eligible studies for inclusion in the final data analysis were those evaluating the efficacy of first-line protocols for canine multicentric lymphoma. Exclusion criteria were studies

describing dogs with extranodal lymphoma, dogs undergoing rescue treatment, or dogs for which treatment efficacy was not recorded.

After the initial search, article titles and abstracts were first evaluated for relevance and potential exclusion, then the studies included for manuscript review were subjected to full article review. The resulting list was therefore screened for non-research articles, duplicates, case reports and irrelevant references.

Two authors were assigned to a time-period as follows: 1999-2001 MD and OAG, 2002-2004 IG and JH, 2005-2007 TH and GL, 2008-2011 LM and EM, 2012-2014 DS and GAP. Selected papers were independently reviewed on the basis of the selected criteria by the two authors for each assigned time period and a consensus on the requested information was reached.

Data extraction

Studies were selected based on completeness of data and inclusion criteria only. From eligible articles, the following data were extracted: study characteristics (authors, nationality, publishing year, journal), study design (prospective versus retrospective, randomized versus non-randomized, controlled versus non-controlled), recruitment period, recruiting practices/ institutions, disease (all histotypes versus B-cell lymphoma versus T-cell lymphoma versus specific histotype), number of enrolled dogs, staging work-up (including complete blood count and serum biochemical profile, urinalysis, thoracic radiographs, abdominal radiographs, abdominal ultrasound, fine-needle aspirate of liver and spleen, bone marrow aspirate, flow cytometry to quantify peripheral blood and bone marrow infiltration, others), diagnosis (histological review with or without immunohistochemistry, cytological review, flow

cytometry), type of chemotherapeutic protocol (drugs used, duration), type of remission assessment (physical examination and subjective assessment of lymph node size reduction/ enlargement, with or without confirmative cytology, flow cytometry, PARR), duration of first remission, and survival time.

Any uncertainty about the inclusion of data from any article was resolved with a consensus meeting. No attempt was made to contact authors for additional information.

Descriptive analysis

Descriptive analysis was performed to present the proportion of studies with each characteristic. Given the small sample size and heterogeneous study methodologies, no statistical comparisons were performed.

Agreement by the Editors and Participants of the European Canine Lymphoma Network

The European Canine Lymphoma Network (ECLN) is a network created in 2009 with the aim of establishing cooperation among different institutions working on canine lymphoma across the fields of diagnosis and therapy.[12] The definition of common guidelines and approaches is one of the main goals of ECLN. This review was submitted to the 25 Editors and Participants of Workgroup 2. The review was planned to be submitted to a peer-reviewed journal only if at least 75% of the participants agreed on its content.

Results

The initial search yielded over 508 references, many of which were not specifically relevant to our topic. After the exclusion of irrelevant studies, 63 articles that appeared relevant to our aim and that met all study criteria were identified and fully reviewed.[4,10,13-72] The main characteristics of the included studies are summarized in Table 1.

Among these studies, 40 (63.5%) were from the USA, 9 (14.3%) were from Italy, 3 (4.8%) were from Germany, 3 (4.8%) were from Brazil, 2 (3.2%) were from Japan, 2 (3.2%) were from UK, 2 (3.2%) were from The Netherlands, 1 (1.6%) was from France, and 1 (1.6%) was from Poland.

Forty-five (71.4%) studies were conducted in single centres, 7 (11.1%) were multicentre studies and 6 (9.5%) were undertaken by two centres. The number of recruiting practices was not stated in 5 (7.9%) studies.

Thirty-seven (58.7%) studies were conducted prospectively, 7 of which were randomized controlled trials comparing chemotherapy alone with chemotherapy and steroids, chemotherapy alone and chemo-immunotherapy, chemotherapy alone and chemotherapy plus total body hyperthermia, chemotherapy plus control diet and chemotherapy plus experimental diet, or two different chemotherapy protocols. Three studies were Phase 1 clinical trials. Twenty-five (39.7%) studies were retrospective and the design of 1 (1.6%) study was unclear.

The median number of dogs per study was 46 (mean, 58; range, 7-456; IQR, interquantile range, 63).

Forty-nine (77.8%) studies included all lymphoma histotypes; 10 (15.9%) studies focused on B-cell lymphomas (3 specifically on high-grade B-cell

lymphoma and 2 on diffuse large B-cell lymphoma, DLBCL); 4 (63.5%) focused on T-cell lymphoma (1 specifically on high-grade T-cell lymphoma) (Figure 1).

Depending on the study, dogs had diagnostic assessment of disease by cytological review only (n=12; 19%), histological review only (n=17; 27%), cytology or histology (n=20; 31.7%), cytology and histology (n= 13; 20.6%), whereas the diagnostic method was not stated in 1 (1.6%) study.

Immunophenotype of disease was determined either by flow cytometry or by immunohistochemistry or by PARR in 47 (74.6%) of the 63 studies examined. Immunophenotype of disease was determined in all dogs in 29 (46%) studies, in the majority to half of the cases in 5 (7.9%) studies, and only occasionally (less than 50% of cases) in 13 (20.6%) studies.

The evaluation of disease extent differed significantly among studies. In 52 (82.5%) studies, staging work-up was described, while in 11 (17.5%) studies the tests performed to assess disease extent were not mentioned.

Considering the 52 studies in which staging was described, the most commonly suggested tests included a complete blood cell count (CBC), serum biochemical profile (83.1%), and/or urinalysis (100%), thoracic radiographs (82.7%), abdominal radiographs (28.8%), abdominal ultrasound examination with or without fine-needle aspiration of liver and spleen regardless of their sonographic appearance (59.6%), and bone marrow evaluation (73.1%). In some studies, the following tests were also performed: serology for infectious diseases (3.8%), and echocardiography and/or electrocardiography (9.6%).

For the purpose of this analysis, staging procedures were grouped in the following categories: minimum work-up (including a CBC and serum biochemical profile and/or radiography or ultrasound, and/or bone marrow

evaluation; 25 [39.7%] studies) or full staging (including a CBC and serum biochemical profile, thoracic radiography, abdominal ultrasound, and bone marrow evaluation; 27 [42.8%] studies) (Figure 2). When specifically focusing on studies in which a full-staging was suggested, tests were not always performed on all dogs.

The most commonly used first-line treatment protocols included vincristine, cyclophosphamide, doxorubicin, and prednisone, with or without other drugs, radiation therapy or immunotherapy (CHOP-based protocols; 45 studies, 71.4%). Fourteen (22.2%) papers evaluated the efficacy of other drugs or combinations of drugs. The adopted protocol was not described in 4 (6.3%) studies.

The duration of the chemotherapeutic protocols was described in 49 (77.8%) studies, and not reported in 8 (12.7%) studies. In 6 (9.5%) studies, the duration of the protocol depended on treatment response and was therefore variable. When described, the median duration of the chemotherapeutic protocol was 19 weeks (range, 4 to 130 weeks; IQR, 12).

Regarding treatment efficacy, if response to treatment was generically described as “regression of measurable tumours”, it was assumed that peripheral lymph nodes were at least measured. Thus, for the purpose of this review, this type of remission assessment was grouped into the category “subjective or radiological/sonographic measurement of peripheral lymph nodes”. The methods for assessing treatment response varied greatly among studies. In 41 (65.1%) studies, treatment response was based on subjective or radiological/sonographic measurement of peripheral lymph nodes; in none of

them, confirmative nodal cytology was described as mandatory. In 2 (3.2%) studies, a complete end-staging was carried out, including bloodwork, urinalysis, imaging and confirmative cytology. In 9 (14.3%) studies, minimal residual disease analysis was carried out, including flow cytometry and/or PARR. Finally, the methods were not described in 11 (17.5%) studies (Figure 3).

The endpoint remission duration was described in 57 (90.5%) studies; the endpoint survival was reported in slightly fewer studies (n=52; 82.5%).

Discussion

For each dog with suspected multicentric lymphoma, the overall goal is a timely diagnosis and administration of appropriate therapy. Needless to say, accurate staging influences management decisions and predicts prognosis for cancer patients in general. Also, clinical staging procedures allow determination of a patient's response to therapy. Finally, clinical stage evaluations serve an important role in allowing the comparison of treatments between studies.

The purpose of this work was to review the last 15 years of published literature to determine to what extent different approaches to evaluate treatment efficacy in the first-line setting were comparable. To the authors' knowledge, there are no other published systematic reviews assessing the methods used for staging canine lymphoma at diagnosis and post treatment.

This systematic review identified a total of 63 articles that satisfied the search criteria. The total number of dogs in the current systematic review is relatively large, with a median 46 dogs per study.

Based on the results of the current review, certain points of controversy were found.

First, there was significant variability across studies concerning histotypes. The greatest majority of studies have been severely hampered by the admixture of a variety of lymphoma subtypes in the analysis of outcome, making it difficult to assess the clinical efficacy of any given treatment. Indeed, it has been well documented that canine lymphomas encompass a group of types of tumors, with different biologic behaviors, patterns of chemosensitivity and treatment responses.[1,2] Thus, clinical trial results need to be interpreted in the context of the distribution of histologic subtypes treated. This, in turn, complicates the assessment of chemotherapy efficacy, making it impossible, in studies describing mixed lymphoma subtypes, to determine whether high or low response rates are due to the specific treatment or to the specific population under study. Only 2 out of the 63 studies evaluated a single lymphoma subtype.

Second, there were striking differences in the criteria for the diagnosis and the extent of the staging procedures. These differences inevitably have an unquantifiable influence on the patients' final outcome, and preclude meaningful comparisons between studies. Briefly, in 17.5% of the studies the staging work-up was not described. Furthermore, almost half of the studies relied on a minimum work-up. Unfortunately, to date no single diagnostic algorithm sufficiently addresses the complexity and variation in disease patterns of canine

lymphoma. Furthermore, local expertise and financial resources can also influence the approach taken. Doubtless, the different opinions concerning the minimum criteria for the diagnosis of canine lymphoma do result in differences in patient selection for different chemotherapeutic protocols and therefore do bias treatment outcome.

Third, the comparability of efficacy between studies was also hampered by differences in response assessment criteria employed.

The importance of response assessment criteria is well described in the literature: recently, the VCOG developed a consensus document, dictating guidelines to standardize definition of normal lymph node size, when and how responses should be assessed, and definitions for response categories and endpoints.[8] However, cytological and molecular diagnostic techniques allow one to state that the VCOG guidelines would tend to overstate complete remission rates and understate progression rates.[8] Indeed, most of the limitations of this document reside in the inter- and intra-observer variability of physical examination, rendering the guidelines not suited for end-staging; furthermore, they do not allow assessment of MRD. A recent study has indeed shown presence of MRD by PARR despite clinical remission in 9 of 12 (75%) dogs with diffuse large B-cell lymphoma.[9] As a matter of fact, despite the ease and practicality of lymph node measurement, the VCOG guidelines have not been validated in clinical and therapeutic studies.

According to the results obtained here, a good proportion of studies (17.5%) did not describe the methods used for evaluating treatment response at all. The majority of studies relied on subjective or radiological measurement of peripheral lymph nodes, whereas few studies defined treatment response

based on MRD evaluation. Although the induction of clinical remission is associated with clinical benefit, RECIST criteria are restricted to measuring tumor size, being insensitive to changes in tumor load in other matrices (such as peripheral blood, bone marrow and abdominal organs), and may therefore overestimate the anti-tumor treatment effect.

In this study it was shown that the absence of accurate diagnostic work-up during the initial and the end-staging may be one of the confounding factors leading to controversial results and different rates of success of antitumoral treatment in the different studies. Clearly, standardization of staging techniques, both initially and after treatment, is needed to decrease, if not eliminate, variability due to selection bias. Until the validity and reliability of measurement tools are ensured, it cannot be accurately determined which of the published treatment protocols will benefit lymphoma dogs. Awareness of these effects for patient selection and for treatment outcome may help in the design of future clinical trials. These trials will require international collaboration and should ideally be designed following multidisciplinary clinical input and include dogs classified according to histological guidelines to ensure homogeneous enrolment.

The participants in the Clinical Working Group of ECLN make the following concluding observations and recommendations.

While the shortcomings of retrospective studies are familiar to all, such clinical studies describing historical actions to real patients will always be of value to our understanding of treatment and disease.

When clinical information concerning canine nodal lymphoma is gained prospectively, thought must be given to the utility of that information for the scientific community at large.

For all dogs enrolled in prospective studies, optimal diagnosis, clinical stage evaluation and response evaluation criteria should comprise as a minimum:

Diagnosis: WHO classification of lymphoma type and/or flow cytometry and cytomorphological analysis to define B/T immunophenotype and morphological subtype within the limits of what is possible using those diagnostic modalities. For the histopathological diagnosis of lymphoma, lymph node excision biopsies (lymphadenectomy) rather than core biopsies are regarded as standard of care.

Clinical Stage: Complete blood count and smear evaluation; thoracic and abdominal imaging (x-ray, ultrasound, CT/MRI as appropriate); cytology of splenic and hepatic aspirates, and bone marrow evaluation prior to initiation of therapy.

Response Evaluation: Two to four weeks following administration of final chemotherapy treatment for discontinuous protocols or four to six months after initiation of therapy for continuous protocols: complete blood count and smear evaluation; thoracic and abdominal imaging (x-ray, ultrasound, CT/MRI as appropriate); cytology of splenic and hepatic aspirates, bone marrow evaluation, and MRD monitoring.

It is recognized that these observations and recommendations are pertinent in the present; future discoveries and trends should lead to their modification. By achieving conformity as suggested, such progress, it is hoped, will be made faster.

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Captions to figures

Figure 1. Pie chart showing the distribution of disease types in dogs enrolled in the 63 studies. (DLBCL: diffuse large B-cell lymphoma).

Figure 2. Pie chart showing the staging methods according to the 63 studies.

Figure 3. Pie chart showing the methods used to assess treatment response according to the 63 studies. (LN: lymph node).

Table 1. Characteristics of included studies (chronologic order).

Author (n)	Study type	Disease	Staging methods				Diagnosis methods			Remission assessment			
			B+U	IM	BM	Other*	C	H	PH	LN meas	C	B+IM	MRD
Piek et al 1999 (117)	R	All histotypes	NR				x	(or) x	no	x	no	no	no
Larue et al 1999 (42)	P	All histotypes	NR				no	x	no	x	no	no	no
Phillips et al 2000 (41)	P	All histotypes	x	x	x	no	no	x	x	x	no	no	no
Ogilvie et al 2000 (32)	P	All histotypes	x	x	x	no	no	x	no	x	no	no	no
Chun et al 2000 (49)	P	All histotypes	x	x	x	no	no	x	OCC	NR			
Boyce et al 2000 (75)	NR	All histotypes	x	x	OCC	no	x	(or) x	no	x	no	no	no
Moore et al 2001 (82)	R	All histotypes	x	OCC	OCC	no	x	(or) x	no	x	no	no	no

Dobson et al 2001 (49)	P	All histotypes	x	x	OCC	no	no	x	x	x	no	no	no
Garrett et al 2002 (53)	P	All histotypes	x	x	x	no	x	OCC	no	NR			
Jagielski et al 2002 (43)	R	All histotypes	x	x	x	no	no	x	no	x	no	no	no
Mutsaers et al 2002 (33)	P	All histotypes	x	x	x	no	no	x	no	x	no	x (IM only)	no
Morrison-Collister et al 2003 (94)	R	All histotypes	X	x	x	no	no	x	MOST	x	no	x	no
Moore et al 2003 (10)	P	All histotypes	X	x	x	no	no	x	MOST	x	no	no	no
Ponce et al 2004 (57)	R	All histotypes	x	x	x	no	x	x	x	x	no	no	no
Ricci Lucas et al 2004 (7)	P	All histotypes	x	x	x	no	x	x	no	x	no	no	no
Williams et al	P	All	x	x	OCC	x	x	(or)	x	x	no	x	no

2004 (52)		histotypes						x					
Gustafson et al 2004 (8)	P	All histotypes	x	x	x	no	x	x	x	x	no	no	no
MacDonald et al 2005 (115)	R	All histotypes	x	x	x	no	no	x	x	NR			
Simon et al 2006 (77)	P	All histotypes	x	x	OCC	x	x	(or) x	MOST	x	no	no	no
Turner et al 2006 (21)	P	All histotypes	x	x	x	no	no	x	no	x	no	no	no
Siedlecki et al 2006 (39)	R	All histotypes	x	x	OCC	no	x	(or) x	OCC	x	no	no	no
Turek et al 2007 (52)	P	B-cell	x	x	x	no	no	x	x	x	no	no	no
Hosoya et al 2007 (101)	R	All histotypes	x	x	OCC	no	x	(or) x	OCC	x	no	no	no
Kaiser et al 2007 (96)	R	All histotypes	x	MOST	OCC	no	x	(or) x	no	x	no	no	no
Gavazza et al	R	All	x	no	x	x	x	no	OCC	NR			

2008 (114)		histotypes											
Marconato et al 2008 (17)	P	All histotypes	x	x	x	x	x	no	x	x	x	x	x
Merlo et al 2008 (20)	P	All histotypes	x	x	no	no	x	no	no	x	no	no	no
Rebhun et al 2008 (31)	R	All histotypes	x	x	x	no	no	x	x	x	no	x	no
Simon et al 2008 (106)	P	All histotypes	x	x	OCC	x	x	x	OCC	NR			
Gavazza et al 2009 (114)	R	All histotypes	x	no	x	x	x	no	OCC	x	no	no	no
Miller et al 2009 (84)	R	All histotypes	NR				x	(or) x	OCC	NR			
Brodsky et al 2009 (50)	R	T-cell	x	x	OCC	no	x	(or) x	x	x	no	no	no
Daters et al 2010 (65)	P	All histotypes	x	x	x	no	x	x	no	x	no	no	no
Lori et al 2010	P	All	x	OCC	OCC	no	x	(or)	OCC	x	no	no	no

(32)		histotypes						x					
Marconato et al 2010 (50)	P	All histotypes	x	x	x	x	x	no	x	x	x	x	no
Rassnick et al 2010 (66)	P	All histotypes	x	x	x	no	no	x	x	x	no	x	no
Sorenmo et al 2010 (119)	R	All histotypes	x	x	x	x	x	no	OCC	x	OCC	NR	no
Yamazaki et al 2010 (17)	P	All histotypes	NR				x	no	x	x	no	no	x
Zenker et al 2010 (17)	P	All histotypes	x	x	OCC	no	x	OCC	no	x	no	no	no
Sato et al 2011 (29)	P	B-cell high grade	x	x	no	no	x	no	x	x	no	no	no
Marconato et al 2011 (127)	R	All histotypes	x	x	x	x	x	no	x	x	no	no	no
Perry et al 2011 (26)	R	All histotypes	x	no	OCC	x	no	x	MOST	NR			
Flory et al 2011	R	All	x	OCC	OCC	no	x	(or)	OCC	NR			

(95)		histotypes						x					
Rebhun et al 2011 (24)	R	T-cell (intermediate or high grade)	x	x	x	no	x	(or) x	x	x	no	no	no
Sorenmo et al 2011 (83)	P	B-cell	x	x	x	no	x	x	x	x	x	x	no
O'Connor et al 2012 (8)	P	B-cell	NR				x	x	x	NR			
Silver et al 2012 (19)	P	All histotypes	x	x	no	no	NR			x	no	no	no
Willcox et al 2012 (19)	P	B-cell	NR				x	(or) x	x	no	no	no	x
Vail et al 2012 (19)	P	All histotypes	x	OCC	OCC	no	no	x	MOST	x	no	no	no
Gentilini et al 2013 (8)	R	B-cell	NR				x	no	x	x	no	no	x
Sato et al 2013	P	B-cell high	x	x	no	no	x	no	x	x	no	no	x

(36)		grade											
Valli et al 2013 (456)	R	All histotypes	NR				no	x	x	NR			
Marconato et al 2013 (46)	P	B-cell high grade	x	x	x	x	x	OCC	x	x	x	x	x
Elliott et al 2013 (97)	R	All histotypes	x	MOST	OCC	OCC	x	(or) x	OCC	x	no	no	no
Burton et al 2013 (31)	R	All histotypes	NR				x	(or) x	OCC	x	no	no	no
Zandvliet et al 2013 (81)	P	All histotypes	x	OCC	x	OCC	x	no	x	x	no	no	no
Warry et al 2014 (14)	P	T-cell high grade	NR				x	(or) x	x	no	no	no	x
Avery et al 2014 (67)	R	T-cell	OCC	OCC	OCC	no	x	(or) x	x	NR			
Marconato et al 2014 (19)	P	DLBCL	x	x	x	no	x	x	x	x	x	no	x
Aresu et al 2014	P	DLBCL	x	x	x	no	x	x	x	x	x	x	x

(14)													
Mutz et al 2015** (77)	R	All histotypes	x	x	OCC	no	x	(or) x	OCC	x	no	x	no
Lucas et al 2015** (15)	P	All histotypes	x	x	x	no	x	x	x	x	no	no	no
Childress et al 2015** (15)	P	All histotypes	NR				x	(or) x	no	x	no	no	no

n: number of dogs, P: prospective, R: retrospective, B+U: blood and urinalysis, IM: imaging (thoracic radiography and/or abdominal radiography and/or abdominal ultrasound), BM: bone marrow evaluation, C: cytology, H: histology, PH: phenotype assessment, LN meas: subjective or radiological measurement of peripheral lymph nodes, MRD: minimal residual disease

NR: not reported, OCC: occasionally (<50% of cases), MOST: most cases (>50%)

* Other: infectious disease serology or cardiac evaluation or fine-needle aspiration of liver and spleen regardless of their sonographic appearance

** The papers published in 2015 were available for early view already when this review was started and were therefore included in the analysis.

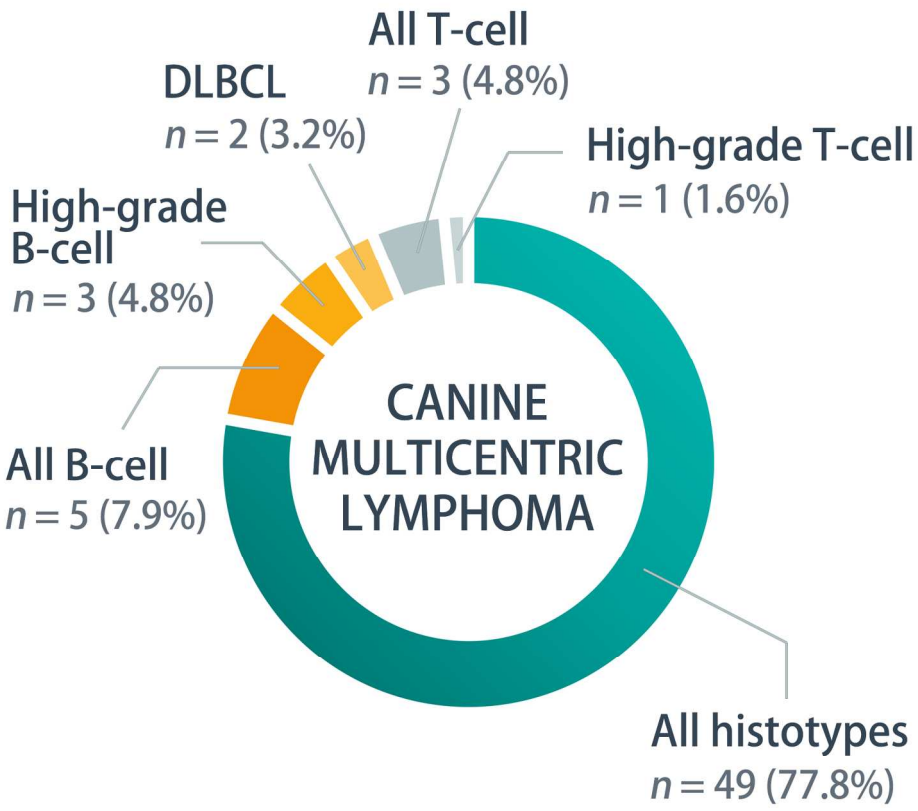

Figure 1. Pie chart showing the distribution of disease types in dogs enrolled in the 63 studies. (DLBCL: diffuse large B-cell lymphoma).
167x149mm (300 x 300 DPI)

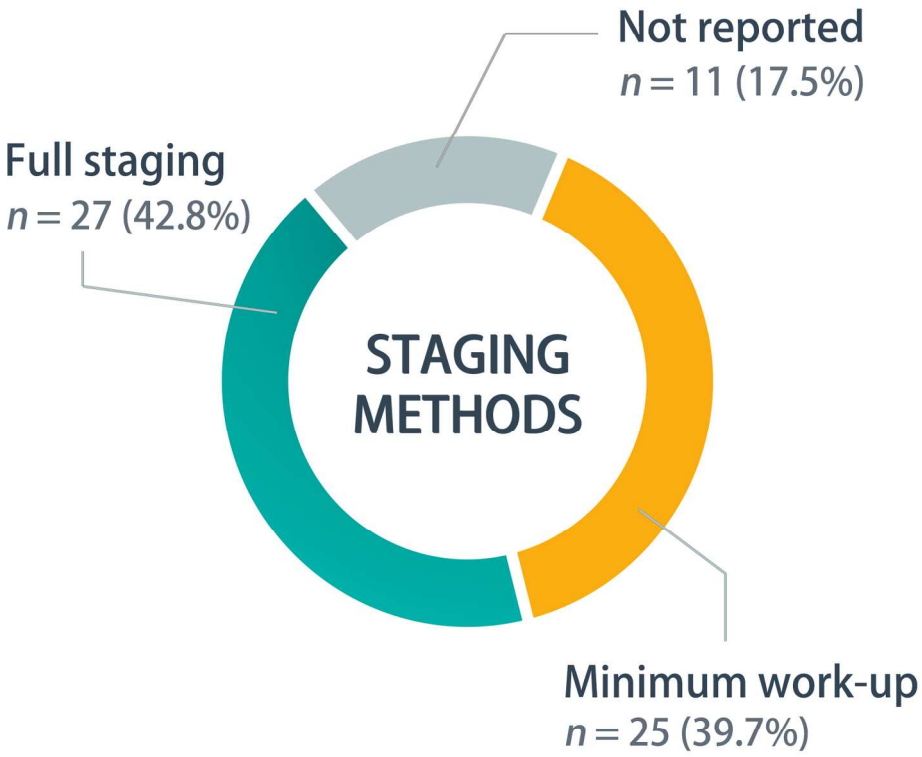

Figure 2. Pie chart showing the staging methods according to the 63 studies.
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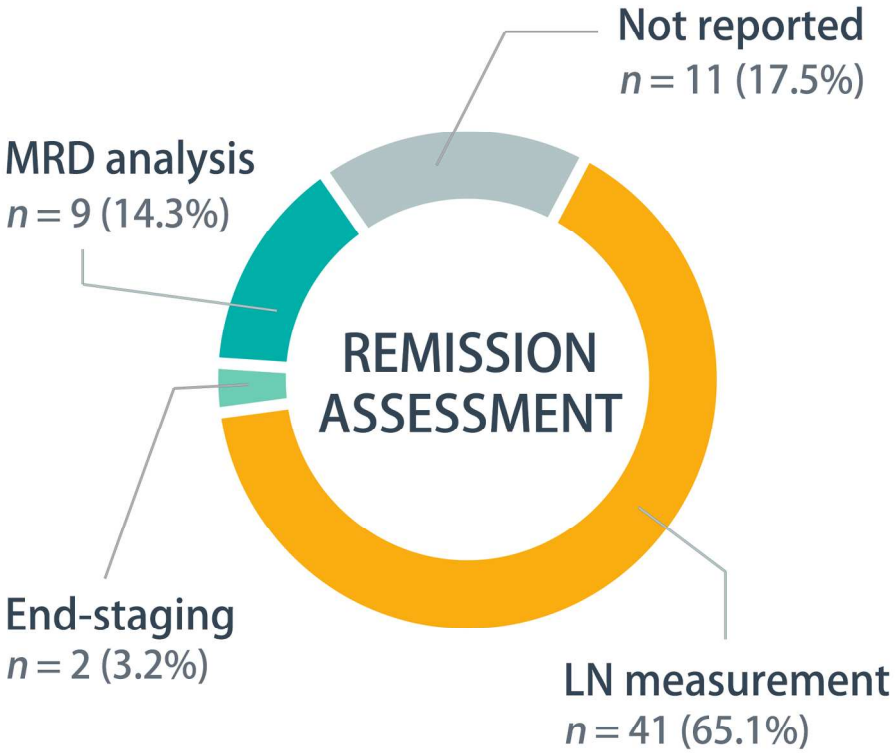

Figure 3. Pie chart showing the methods used to assess treatment response according to the 63 studies. (LN: lymph node).
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