Surgery in Castleman's Disease

A Systematic Review of 404 Published Cases

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Objectives: We undertook a systematic review of 404 published cases of Castleman's disease to identify the role of the surgeon beyond assistance in tissue-based diagnosis.

Background: Castleman's disease is a rare primary disease of the lymph node caused by infection with herpesviridae. Little is known about the role of surgery in this condition.

Data Sources: Medline, Embase, Cochrane Database of Systematic Reviews, ISI Thompson Web of Knowledge, and hand search of articles' bibliography.

Study Selection: Of the 1791 citations identified through the initial electronic search and screened for possible inclusion, 488 articles were retained after title and abstract reviews. Of these, 239 were accepted for this review.

Data Extraction: A complete dataset containing age, gender, centricity (unicentric vs multicentric), histopathologic type (hyaline vascular [HV] vs plasma cell [PC]), anatomical location of the only focus in unicentric Castleman's disease (UCD) or the dominant focus in multicentric Castleman's disease (MCD), nature of the surgical approach (resective vs diagnostic), and outcome (disease-free survival [DFS] vs death due to disease) was extracted.

Results: A resective or debulking surgical approach was described in 77.0% of all patients, but was far more common in unicentric (262/278; 94.2%) than multicentric (49/126; 38.9%) disease (χ^2 146.8; $P < 0.0001$). Unicentric disease had a significantly higher overall survival (95.3% vs 61.1%; χ^2 55.7; $P < 0.0001$), 3 year DFS (89.7% vs 55.6%; χ^2 27.8; $P < 0.0001$), and 5 year DFS (81.2% vs 34.4%; χ^2 28.6; $P < 0.0001$) than multicentric disease. Failure to treat unicentric disease by resective surgery resulted in a significant mortality (17.6% vs 3.8% χ^2; $P < 0.05$). In multicentric disease, outcomes are comparable between debulking surgery alone, immunochemotherapy alone, or a combination of both (28.0% vs 28.9% vs 50.0%; $P =$ nonsignificant).

Conclusions: Surgery is the gold standard for treatment of unicentric Castleman's disease. The role of debulking surgery in human immunodeficiency virus (−) MCD needs to be evaluated in prospective studies.

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Castleman's disease was first described in a single case in 1954[1] followed by a small series in 1956.[2] It is a rare lymphoproliferative disorder caused by human rhadinovirus infection of the B-cell pool and the lymphovascular compartment of lymph nodes.[3] Pathological classification differentiates unicentric and multicentric disease on the basis of the anatomical distribution of disease.[4] Histological classification differentiates hyaline vascular (HV) versus plasma cell (PC) disease according to the pattern of destruction of normal lymph node morphology.[5] Much light has recently been shed on viral pathogenesis and the role of immunochemotherapy in human immunodeficiency virus (HIV) related Castleman's disease.[6] Nevertheless, the majority of published cases were observed in patients without immunodeficiency syndrome. The surgeon is an essential member of the treating team and usually becomes involved when biopsy is indicated in the presence of a patient with lymphadenopathy, suspicious lesions in chest or abdomen, B-symptoms, and often a working diagnosis of lymphoma or other systemic disease. In absence of controlled trials, larger surgical case series or systematic reviews, it is not known if the role of surgery in Castleman's disease exceeds mere diagnostic sampling. This detailed case analysis aims to explore the wealth of 404 published case reports in patients with Castleman's disease and describes the impact of surgery on long-term outcome.

METHODS

Literature Search Strategies

A systematic search was conducted of the published literature on Castleman's disease. Databases searched included Medline, Cochrane Database of Systematic Reviews, and ISI Thompson Web of Knowledge using the search term "Castleman's disease" in September 2009. Searches were conducted with language restriction; these included English, German, French, and Spanish articles only. Hand search of bibliographies of these articles was also performed using the ISI Thompson Web of Knowledge Citation report, and further articles were retrieved. The search identified 1791 articles in English, French, Spanish, and German. Of the 1791 citations identified through the initial electronic search and screened for possible inclusion, 488 articles were retained after title and abstract reviews giving a total of 1000 patients with Castleman's disease (556 patients from case reports, 444 patients from small case series). Of these, 239 articles were accepted for this review, giving a total of 404 patients.

Inclusion Criteria

Articles were selected if the abstract contained the term Castleman's disease in the form of case reports, other controlled or comparative studies, or small case series. In the case of duplicate publications, the latest and most complete study was included. The inclusion criterion was unambiguous evidence of Castleman's disease in the form of a histology description demonstrating HV, PC, or mixed variant.[4] The case reports and case series included in this analysis are referenced in Supplemental Digital Content 1, available at: http://links.lww.com/SLA/A207. We excluded patients with positive HIV status where reported and also patients presenting with isolated POEMS, that is, a rare PC dyscrasia presenting with polyneuropathy, organmeglay, endocrinopathy, monoclonal gammopathy, and skin changes, who failed to meet the diagnosis of Castleman's disease.

Data Extraction and Synthesis

Data were extracted by one researcher and checked by another using standardized extraction tables developed a priori. Data were pooled as individual cases in a single contingent statistical package for the social sciences (SPSS) table. Outcome analysis was performed in the set of 404 patients for whom a complete dataset containing age, gender, centricity (unicentric vs multicentric), histopathologic type (HV vs PC), anatomical location of the only focus in unicentric

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Castleman's disease (UCD) or the dominant focus in multicentric Castleman's disease (MCD), nature of the surgical approach (resective vs diagnostic), and outcome (disease-free survival vs death due to disease) was available.

Values for mean, median, standard deviation, 95% confidence intervals (CI), risk ratio, odds ratio, Pearson's correlation coefficient, 2-sided significance levels, and Kaplan-Meier statistics were calculated using SPSS software version 16.0.

A patient was treated as lost to follow-up for purposes of Kaplan-Meier analysis at the end of the reported observation time. *Overall survival* is defined as outcome survival versus death due to disease. This group comprised 404 patients (UCD, n = 278; MCD, n = 126). Three-year and 5-year *disease-free survival* (DFS) is defined as outcome survival versus death in all patients for whom follow-up information was available at 36 and 60 months, respectively. The 3-year DFS comprised n = 179 patients (UCD, n = 107; MCD, n = 72). The 5-year DFS comprised n = 127 patients (UDC, n = 69; MDC, n = 58). Overall survival for 404 patients (UCD, n = 278; MDC, n = 127) is also presented with a Kaplan-Meier analysis curtailed at 10 years, which disregards all follow-up events reported later than 10 years to exclude a patient reporting bias of later events. This group was also used for all further analysis.

The term *resective surgery* is used to describe those surgical interventions undertaken to completely resect unicentric disease. In multicentric disease, the term resective surgery equals that of debulking surgery, that is, when excision of the majority of diseased tissues was achieved as opposed to any procedure merely attempting to obtain tissue for a diagnosis.

Diagnostic surgery was defined as a wedge biopsy of a lymph node or a solid organ in unicentric disease or excision of one of many lymph nodes or rarely part of an organ in multicentric disease with the majority of diseased tissue remaining in the patient.

The term *dominant focus of disease* is mostly used in the context of multicentric disease. Many such patients have more than one region involved with disease, but the volume of such disease outside the dominant focus can be very limited. Such patients have then eventually been subject to a debulking surgical procedure trying to eliminate most detectable disease by an approach to one or more regions. For the purpose of depiction, such patients have been shown as localized where the dominant focus was described (Fig. 1). In the context of unicentric disease, the term dominant focus is used for those rare cases, which are multifocal but truly unicentric. These patients present with a dominant diseased lymph node surrounded by a number of smaller satellites.

RESULTS

Since 1954, Castleman's disease has been reported in 1000 patients. We extracted the complete information from case reports and case series. Unfortunately, reporting standards were met with varying stringency. There was a limited number of complete datasets with regard to key items required for analysis. We defined these items as age, gender, centricity (unicentric vs multicentric), histopathological type (HV vs PC), anatomical location of the only focus in UCD or the dominant focus in MCD, kind of surgery performed (resective vs diagnostic), and outcome (disease-free survival vs death due to disease). Only patients without evidence of infection with HIV were included. The HHV8 status was disregarded for this part of the analysis.

A full dataset was available in 404 patients. All data presented throughout this study relate to this dataset unless specified otherwise. Kaplan-Meier analysis was performed in 4 different groups of patients to avoid misinterpretation by an eventual reporting bias related to the length of the observation period (Fig. 2). The cumulative number of patients who died from disease was as follows for UCD and MCD: 12 months (9/22), 24 months (11/26), 36 months (11/32), 48 months (13/36), 60 months (13/38), 72 months (13/41), 84 months (13/41), 96 months (13/41), 108 months (13/41), and 120 months (13/41). The number of patients at risk to die of disease was as follows for UCD and MCD: 0 months (278/126), 12 months (199/86), 24 months (138/57), 36 months (96/42), 48 months (71/30), 60 months (56/22), 72 months (38/15), 84 months (32/11), 96 months (26/10), 108 months (21/9), and 120 months (14/5). A patient was treated as lost to follow-up for purposes of Kaplan-Meier analysis at the end of the reported observation time. Figure 2 demonstrates consistent outcome of Kaplan-Meier analysis for overall survival, 3-year DFS, and 5-year DFS.

The distribution of the solitary (UCD) or dominant (MCD) diseased lymph glands is depicted in the body schemes in Figure 1. Primary organ manifestations in Castleman's disease are rare and have been observed mainly in the spleen (n = 17; all in MCD) and the parotid gland (n = 11, all in UCD). A surgical approach was identified in all patients because the diagnosis of Castleman's disease can only be made by histopathological examination. A resective approach with complete excision or debulking was described in 311 of the 404 patients (77.0%).

Table 2 gives details of the surgical approach and its combination with other therapies such as any form or combination of immunotherapy or chemotherapy (antibody therapy targeting interleukin 6 [IL-6], CD20, or polychemotherapy). All patients included underwent some form of treatment. The description of the surgical approach did not allow an exact identification of access and target related surgery in all cases. We have therefore identified the specific numbers of cases in whom information was provided.

In unicentric disease, far more patients underwent resective as opposed to diagnostic surgery (262 of 278 patients or 94.2%) as compared to multicentric disease (49 of 126 patients or 38.9%). This difference was highly significant (χ^2 146.8 with $P < 0.0001$). In multicentric disease, surgery targeted peripheral lymph nodes more frequently than all other locations combined (107 vs 45 patients), whereas they were less common than visceral approaches in unicentric disease (74 vs 161 patients) (χ^2 31.6 with $P < 0.0001$). Exact information about the surgical access (as opposed to the surgery performed on target) was available in 229 patients. Endoscopic techniques were used in a minority of patients (5 of 68 patients [7.3%] with intrathoracic disease and 3 of 93 patients [3.2%] with intra-abdominal disease).

Regardless of the therapeutic modalities involved, there is a highly significant outcome difference between UCD and MCD (Fig. 2). Table 1 demonstrates that patients with UCD differ highly significantly from those with MCD with regard to every single item assessed. Exact information on the size of the solitary (UCD) or dominant (MCD) diseased lymph glands was available in only 234 patients. Mean size was larger in UCD (n = 213) at 5.5 ± 3.8 cm (95% CI, 5.1–5.9 cm; range 1.0–20.0 cm) than for MCD (n = 21) at 3.8 ± 2.0 cm (95% CI, 2.9–4.7 cm; range: 1.5–10.0) (χ^2 7.7 with $P < 0.01$).

Unicentric and multicentric disease hence constitute 2 separate entities with significantly different clinical characteristics and surgical approach. Thus, we have further analyzed these 2 groups separately with regard to surgery as a single treatment or as a part of multimodal management.

In unicentric disease, long-term outcome was significantly better if patients underwent resective as opposed to diagnostic surgery (Fig. 3). Outcomes were equally better when peripheral lymph nodes were the target of surgery as compared to surgery targeting lymph tissue in either chest or abdominal cavity (Fig. 4). Death due to disease up to 10 years was rare after lymph node excision in axilla (0/13; 0%), groin (0/4; 0%), or neck (1/51; 1.8%). It was significantly more

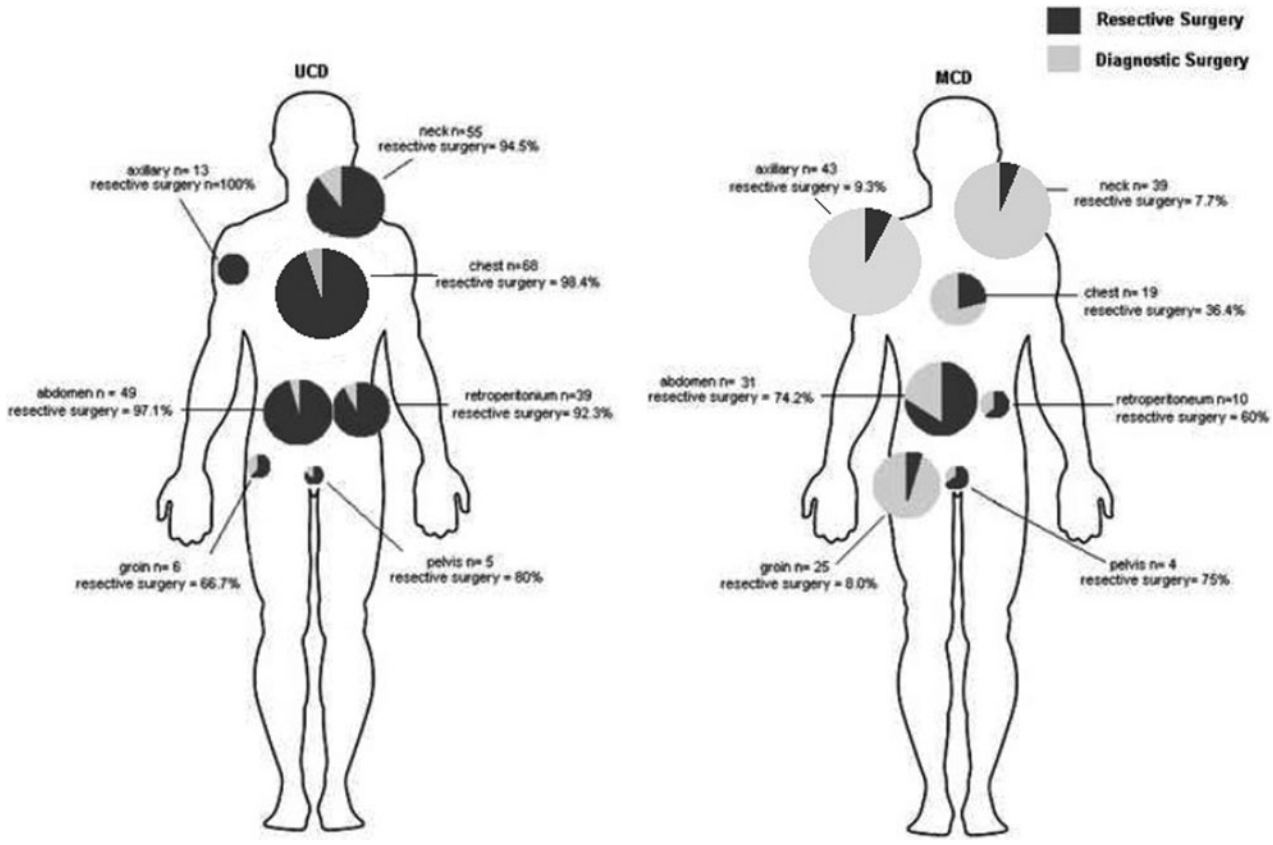

FIGURE 1. Region-specific surgical approach (resective vs diagnostic) in unicentric Castleman's disease (UCD) and multicentric Castleman's disease (MCD). The pie charts indicate the percentage of resective versus diagnostic surgery of each region for the patients with identified surgical approach. The surface of the pie charts indicates the distribution of the single (UCD) (n = 235) or dominant (MCD) (n = 119) focus in 404 patients. Manifestations outside the above areas are not depicted here (n = 43 for UCD; n = 7 for MCD).

common ($P < 0.05$) when the disease was located in the retroperitoneum (4/36; 11.1%), mediastinum (4/66; 6.1%), or abdomen (1/41; 2.4%) and pelvis (0/5; 0%)

Multinomial analysis of outcome relevance of the known clinical characteristic revealed only the kind of surgery performed (resective vs diagnostic) to impact on outcome, whereas age, gender, histopathological type (HV vs PC), and anatomical location were irrelevant (Table 4).

In multicentric disease, there was no long-term outcome benefit if patients underwent resective as opposed to diagnostic surgery (Fig. 5). Death due to disease until 10 years was rare after resective surgery with peripheral lymph node clearance in axilla (0/4; 0%), groin (1/2; 50%), or neck (0/3; 0%). Overall, it was more common when the disease was located in visceral territories as opposed to peripheral lymph node stations, breaking down into the retroperitoneum (1/6; 16.7%), mediastinum (4/7; 57.1%), or abdomen (12/25; 48%) and pelvis (1/3; 33.3%) (P = nonsignificant).

We also present data on a subset of the aforementioned 404 patients: confirmation of a positive infection status with HHV8 in absence of HIV infection and survival data was available in 49 of these 404 patients. All but 3 of these 49 patients (93.9%) suffered from multicentric disease. Resective surgery in terms of a significant debulking procedure was performed in 30 of these patients (61.2%); it was used as the only therapeutic modality in 14 patients (28.6%) and combined with some form of immunotherapy or chemotherapy in 2 patients (4.1%). At 10 years, 19 of these 49 patients were reported to have died of disease (38.8%), of whome 6 of 12 were patients treated with surgery alone (50%) as opposed to 11 of 30 patients treated with immunochemotherapy alone (36.7%) (P = nonsignificant). Comparison of patients with identified HHV8 infection compared to the subgroup with proven negative HHV8 status showed poorer survival in the HHV8 positive group (data not shown).

DISCUSSION

The present review of 404 clinical cases is the first to provide in-depth information on a large retrospective cohort of patients with Castleman's disease. In the past, centricity and histopathologic type have been used as classification criteria of equal importance, and were used in conjunction.[4,5] Our analysis shows that unicentric and multicentric disease are sharply separable entities, with different patient characteristics, presentation, response to therapy, and long-term outcome. Recognition of these entities also sharply defines the surgeon's role and approach in the diagnosis and treatment of Castleman's disease.

In practical terms, it is of pivotal importance to differentiate Castleman's disease from lymphoma and to identify unicentric as opposed to multicentric disease at a clinical level in a stepwise approach. The clinical presentation of Castleman's disease is characterized by typical B-symptoms in conjunction with one (unicentric) or multiple (multicentric) lymph nodes, which are typically spontaneously

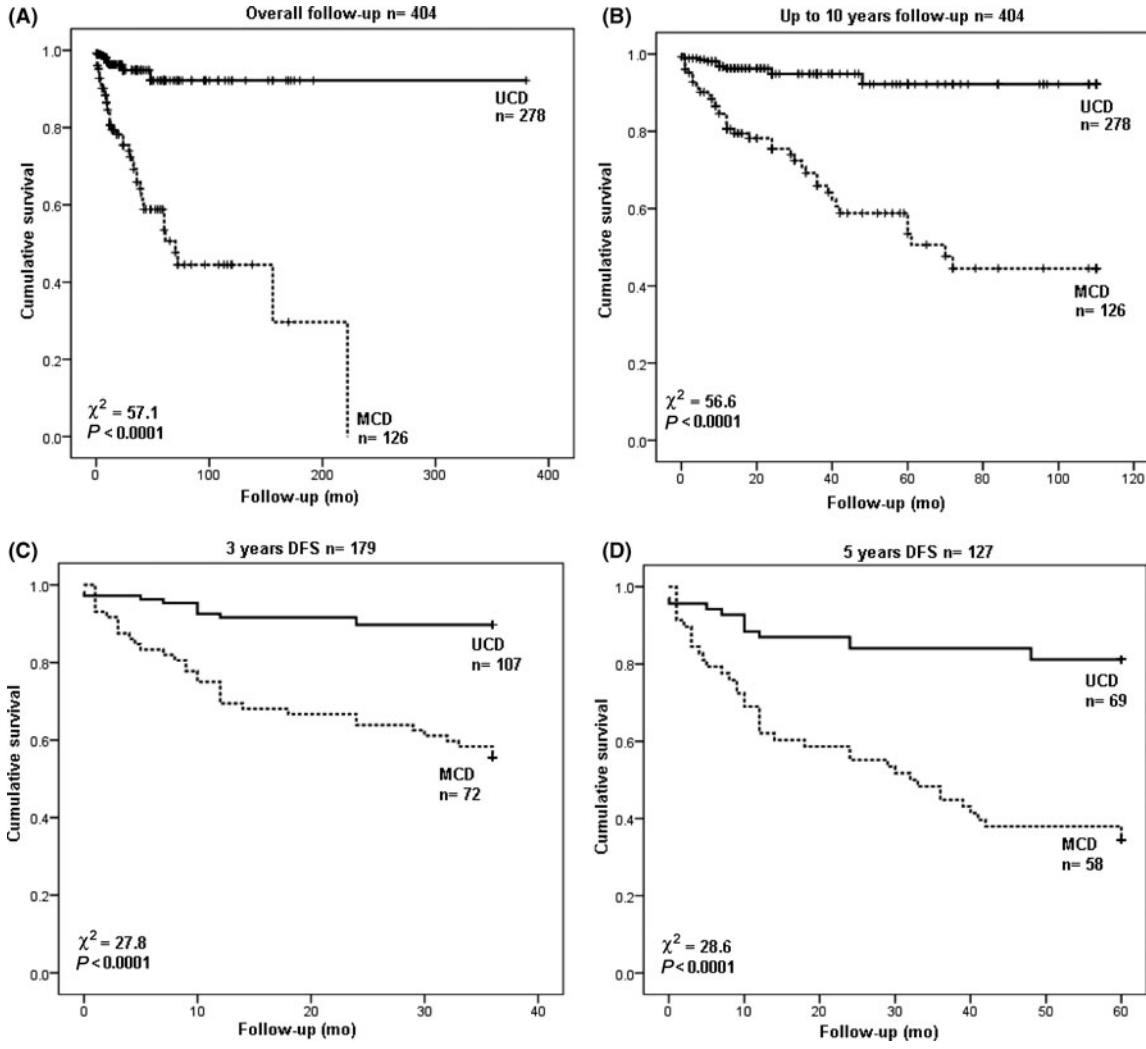

FIGURE 2. Outcome in Castleman's disease depending on centricity. Kaplan-Meier analysis for the outcome death. A: overall survival of the cohort of 404 patients. B: overall survival with Kaplan-Meier analysis restricted to follow-up data up to 10 years. Vertical bars in both graphs (A and B) indicate the point in time for which last follow-up information is reported for an individual patient who is then considered lost to follow-up. C: 3-year disease-free survival (DFS) for 179 patients with complete follow-up data at **3** years. D: 5-year DFS for 127 patients with complete follow-up data at 5 years.

tender and tender to touch. An elevated erythrocyte sedimentation rate and C-reactive protein, leucocytosis, and mild fever may occur. The presentation may indeed relate to focal compression symptoms in unicentric disease. The clinical constellation does not pin point the diagnosis. Lymphoma may be the initial working diagnosis. Elevated serum levels of IL-6 and demonstration of circulating HHV8 particles via polymerase chain reaction can pinpoint the diagnosis, but are neither widely available nor commonly used in clinical practice.[7] In unicentric disease, the lymphadenopathy is unifocal and the swollen lymph node is typically of considerable size with a mean size of 5.7 cm, which is larger than that observed with lymphoma lymph nodes. The critical step is proper classification in the setting of unicentric disease. The patient should undergo clinical examination of all peripheral lymph node stations, including the central and lateral neck, the supraclavicular and dorsal nuchal lymph node stations, the axillae and groins. In cases in which clinical examination is not fully satisfactory, ultrasound should be used to elucidate the situation. Visceral foci of Castleman's disease also need to be excluded. The best entity would be whole-body contrast computed tomographic scan, including neck, chest, abdomen, and pelvis.[8–12] Theoretically, this should have a very high predictive value to either demonstrate or exclude disease in these regions because the minimal size of any reported diseased tissues in either unicentric or mulitcentric disease is greater than 1 cm. If contrast application is contraindicated a whole-body, fluorodeoxyglucose positron emission tomographic scan may provide effective screening.[13–15]

The cause of the markedly different presentation of unicentric and multicentric disease is not clear. It may at least partially be due to differences in the prevalence of viral infection. HHV8 infection has been shown in only 3 patients with unicentric disease,[16–18] of whom one suffered recurrence after excision the primarily involved lymph node and later died from spreading disease.[16]

The histopathological type is of secondary importance, if any, to predict long-term outcome in Castleman's disease. Equally, we

TABLE 1. Clinical Presentation in 404 Patients

Number of patients	UCD 278	MCD 126	χ^2	*P*
Gender				
Female/male	165/113	48/78	15.7	<0.0001
Age (yrs)				
Mean	33.8 ± 17.8	50.0 ± 17.8		
95% CI	31.7–35.9	46.8–53.1	71.6	<0.0001
Range	2.0–84.0	1.0–83.0		
Histopathogenic type				
Hyaline vascular/plasma cell	218/60	32/94	101.1	<0.0001
Location				
Peripheral/visceral	74/161	77/45	31.6	<0.0001
Death due to disease during follow-up up to 10 years				
Yes/no	13/265	41/85	55.7	<0.0001

Unicentric and multicentric diseases differ significantly with regard to each clinical parameters analyzed by 2 × 2 contingency table χ^2 with Yates' correction, 2-tailed analysis.

MCD indicates multicentric Castleman's disease; UCD, unicentric Castleman's disease.

TABLE 2. Treatment modalities and outcomes in 404 patients with UCD and MCD

	UCD, n	MCD, n	χ^2	*P*
Surgery				
Resective/diagnostic	262/16	49/77	142.7	<.0001
Resective Surgery alone				
Yes/no	249/29	25/101	186.5	<.0001
Resective Surgery + immunosuppressive therapy				
Yes/no	13/265	24/102	20.2	<.0001
Immunosuppressive therapy alone				
Yes/no	16/262	77/49	142.7	<.0001
Death due to disease during follow-up up to 10 years				
Yes/no	13/265	41/85	55.7	<.0001

Unicentric and multicentric diseases differ significantly with regards to each different treatment modalities, analyzed by 2 × 2 contingency table χ^2 with Yates' correction, 2-tailed analysis.

MCD indicates multicentric Castleman's disease; UCD, unicentric Castleman's disease.

TABLE 3. Surgical Interventions in 404 Patients With UCD and MCD

Location	Surgery	All Surgeries in UCD[a]	UCD, n (%)	All Surgeries in MCD[a]	MCD, n (%)
Peripheral lymph stations	Resection of dominant lymph node	(No. Operations)	63 (22.7)	(No. Operations)	75 (50.7)
	Systematic regional lymphadenectomy	74	11 (3.9)	77	2 (1.4)
	Resection of dominant lymph node		19 (6.0)		15 (10.1)
Chest	Systematic regional lymphadenectomy	68	49 (17.6)	19	4 (2.7)
	Resection of dominant lymph node		89 (32.0)		28 (18.9)
Abdomen/pelvis	Organ + lymph node resection	93	4 (1.4)	45	17 (11.5)
Other	Other surgery	43	43 (15.5)	7	7 (4.7)
	All operations, n (%)	278	278 (100)	148	148 (100)

[a]In UCD only one surgery per patient has been performed. In MCD a total of 126 patients underwent surgery in 148 sites; 110 patients underwent surgery in only one site and 16 patients in multiple sites.

MCD indicates multicentric Castleman's disease; UCD, unicentric Castleman's disease.

failed to find evidence for its potential use to indicate surgical or conservative therapy regimes. These findings do not support opinions voiced in recent reviews, which suggested to primarily use the histopathogenic type for classification purposes.[5,19,20] Initial Kaplan-Meier plotting in our cohort suggested that HV disease has a better prognosis. However, the marked advantages of patients with HV disease disappeared after stratification for uni- or multicentric disease (see Table, Supplemental Digital Content 2, available at: http://links.lww.com/SLA/A208, which shows a cross-table analysis for each factor entering the outcome analysis in UCD and Table, Supplemental Digital Content 3, available at: http://links.lww.com/SLA/A209, which demonstrates a cross-table analysis for each factor entering the outcome analysis in MCD). In fact, HV disease predominates in unicentric disease (see Table, Supplemental Digital Content 2) and thus seems to relate to a better outcome. However, there is no outcome difference comparing PC and HV type in the patient group with unicentric or multicentric disease (See Figures, Supplemental Digital Content 4, available at: http://links.lww.com/SLA/A210, which

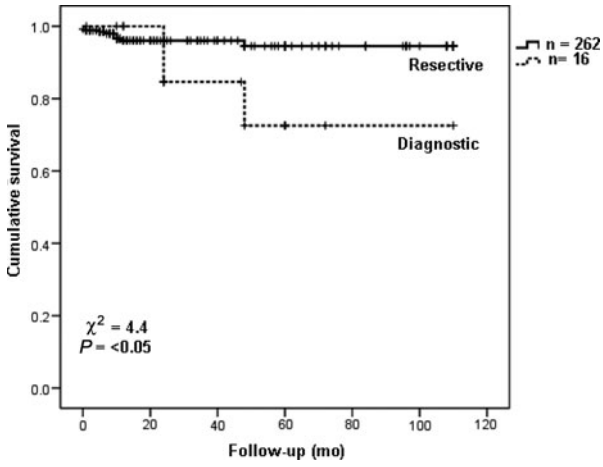

FIGURE 3. Outcome in unicentric Castleman's disease (UCD) patients treated with resective versus diagnostic surgery. The term resective surgery is used to describe those surgical interventions undertaken to completely resect unicentric disease. *Diagnostic surgery* was defined as a wedge biopsy of a lymph node or a solid organ in unicentric disease. Follow-up data up to 10 years was included in the analysis. Vertical bars indicate the point in time for which last follow-up information is reported for an individual patient who is then considered lost to follow-up.

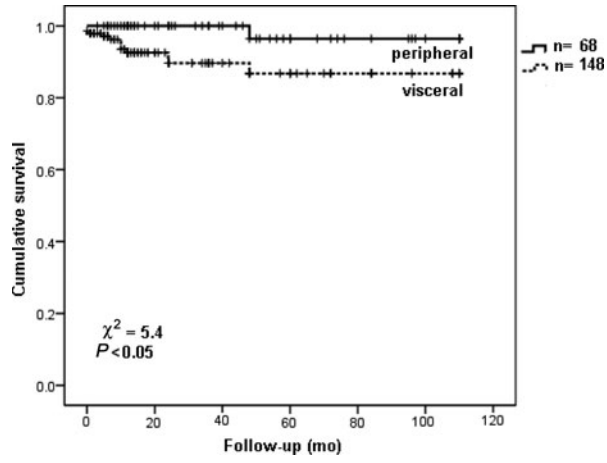

FIGURE 4. Outcome in patients with unicentric Castleman's disease (UCD) after initial resective surgery as sole treatment modality. The cohort of 68 patients with UCD presenting in "peripheral" domains indicates those with lymph node in the neck (n = 51), axilla (n = 13), and groin (n = 4). Visceral denotes the lymph node disease in the chest (n = 66), abdomen (n = 41), retroperitoneum (n = 36), and pelvis (n = 5). Follow-up data up to 10 years was included in the analysis. Vertical bars indicate the point in time for which last follow-up information is reported for an individual patient who is then considered lost to follow-up.

illustrates the outcome differences comparing histopathogenic type in UCD and MCD). The lacking impact of histopathological presentation correlates well with the observation that a rigid 2-tier classification may be somewhat artificial because specimens may show pure HV disease, pure PC disease or any degree of transition between the two, then called mixed type disease.[5] In fact, a significant number of patients demonstrate findings of both histopathological classes or are primarily classified as mixed type (Schulte and Talat unpublished data). This pleiomorphic manifestation on the histopathological level may well relate to gradually expanding viral infection and potentially reflect the specific causative viral agent.[3]

The observation that surgical treatment of Castleman's disease can be curative corresponds with observations in posttransplant lymphoproliferative disorders (PTLD). Unicentric PTLD is a well-recognized virally induced lymphocyte dyscrasia.[21] Surgery may be the cornerstone of therapy where the focus of PTLD is not located in the transplant organ itself or in vital organs.[22] Equally, therapy of Kaposi sarcoma by surgery or other local monotherapy, such as radiation, has been shown to be effective in HIV negative patients.[23]

Unicentric disease responded very well to resective surgery as the sole treatment modality (Figs. 2 and 3). Outcome analysis was performed using generally accepted approaches such as overall DFS and 3- and 5-year DFS. Results of this analysis are consistent in these subgroups and argue against a reporting bias related to the length of reported time of follow-up or significant differences in cohort composition related to follow-up (Fig. 2).

Failure to resect the primary involved lymph node is the only significant predictor for fatal outcome if clinical and histopathological criteria are entered into multinomial regression analysis (Table 4) and a diagnostic "wedge" resection has significantly worse outcome than complete excision of the diseased lymph node (Fig. 3). The surgical approach should aim to resect the primarily involved lymph node with free resection margins, or if a cluster of lymph nodes is involved to perform a loco-regional systematic lymphadenectomy. Excision of the dominant node is the common approach in peripheral nodes, whereas systematic lymphadenectomy was performed in the majority of thoracic surgeries (Table 3). A resective surgical approach is feasible in the vast majority of patients with UCD (Fig. 1). Outcome of such respective surgery is better in peripheral than visceral lymph node territories (Fig. 4). On the basis of the clear outcomes in 278 patients with UCD, it can be concluded that resective surgery with no further multimodal approach is safe and should be considered the gold standard for the treatment of suspected Castleman's disease. In this context, surgery delivers both the establishment of a tissue-based diagnosis and cure of the condition. A visceral location of the dominant disease focus does not preclude a successful surgical approach. Surgical decision making in this setting relates to general principles of surgery, such as general and specific operability, and matters of the technical approach. Under many circumstances, lymphoma may be the initial working diagnosis[24–28] and the surgeon is consulted to gain enough tissue to achieve lymphoma classification. A wedge resection may be the first step, but once a diagnosis of UCD has been established complete resection of the lymph node and/or its surrounding lymph nodes should be pursued to achieve surgical cure.

Multicentric disease presents the surgeon with an entirely different scenario. Faced with the diagnosis, there is no curative indication for surgery because outcomes are at best similar to those obtained with various forms of immunochemotherapy. At present, the role of the surgeon should be limited to gaining tissue by an appropriate biopsy and to debulk dominant foci of multicentric disease in presence of specific organ-related indications such as vascular or airway compromise, massive organomegaly, or bowel obstruction. Similar outcomes of debulking surgery alone compared to immunochemotherapy point toward some usefulness of surgery in multicentric disease. On the contrary, the use of potent antiviral drugs such as valganciclovir[29,30] and valacyclovir alone has produced encouraging results in accordance with the understanding of MCD as

TABLE 4. Results of Multinominal Logistic Regression for the Contribution of Gender, Pathology, Age, Location, and Type of Surgery to Survival Outcomes in 278 UCD Patients

						95% CI for Exp(B)	
Outcome*	**B**	**Standard Error**	**Wald**	**Significance**	**Exp(B)**	**Lower Bound**	**Upper Bound**
Male	0.6	0.6	0.9	ns	1.7	0.6	5.4
PC	0.2	0.7	0.1	ns	0.8	0.2	3.3
Age >31 yrs†	1.2	0.7	3.4	ns	3.5	0.9	12.6
Peripheral	1.9	1.1	3.2	ns	6.6	0.8	51.8
Diagnostic surgery	1.1	0.7	**5.9**	**<0.01**	0.2	0.2	3.3

*The reference category is 1 = death.
†Age dichotomized at the median.
ns: nonsignificant.
B: The estimated multinomial logistic regression coefficients for the model.
Standard Error: The standard errors of the individual regression coefficients for the respective models estimated.
Wald: The Wald χ^2 test that tests the null hypothesis that the estimate equals 0.
Sig are the *P* values of the coefficients or the probability. The probability that a particular Wald test statistic is as extreme as or, more so, than what has been observed under the null hypothesis is defined by the *P* value and presented here.
Exp (B): The odds ratios for the predictors.
Bold values indicate that the results are statistically significant.
PC indicates plasma cell; UCD, unicentric Castleman's disease.

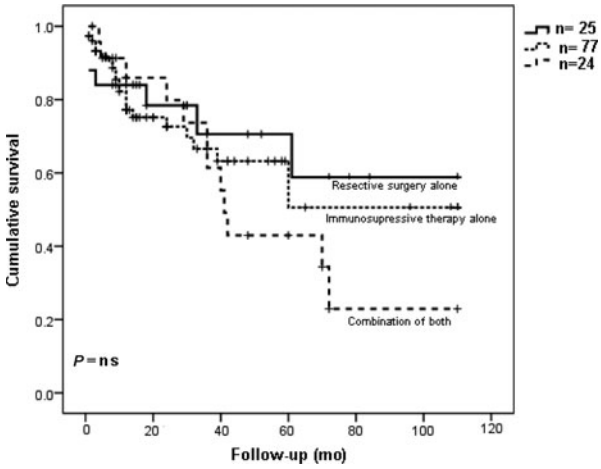

FIGURE 5. Outcome in multicentric Castleman's disease (MCD) patients with different therapeutic approaches. Resective surgery alone refers to those 25 patients who underwent debulking surgery as only treatment. Immunosupression therapy refers to those 77 patients who were treated with monoclonal antibodies to IL-6 or CD20, by conventional or other chemotherapy or any combination hereof. Combination of both refers to those 24 patients who were treated in an adjuvant concept by debulking surgery followed by any form of immunochemotherapy. Follow-up data up to 10 years was included in the analysis. Vertical bars indicate the point in time for which last follow-up information is reported for an individual patient who is then considered lost to follow-up.

an essentially virus-driven disease.[3] Valgancicolvir may have a role as maintenance therapy.[31] Future controlled trials will have to elucidate how multimodal therapy could be optimized: Surgery may help to debulk at an initial stage followed by rituximab combined with chemotherapy for more aggressive disease and eventually followed by antiherpes virus therapy for long-term disease control. Future controlled trials will have to elucidate a potential role of surgery in a multimodal treatment approach in the HIV-negative patient. Rapid advance of combined antiviral therapy approaches is more likely to further patient outcomes than any attempts of extensive surgery.[6,29,30,32]

The authors are aware of the limitations of the current study, which relates to its retrospective nature, possible reporting bias, and limited follow-up information. Creation of a well-maintained internet-based registry holds the potential to significantly enhance data accrual and to provide a platform for much needed prospective randomized interventional studies.

CONCLUSIONS

In summary, we provide evidence that centricity rather than histopathological type impacts on long-term outcome of Castleman's disease. Unicentric and multicentric disease are strikingly different and require a differential therapeutic approach. Resective surgery is the gold standard of treatment in unicentric disease presenting in any organ domain. The established role of surgery in multicentric disease is to obtain tissue for a full histopathological diagnosis of Castleman's disease. The potential benefit of debulking procedures in multicentric disease needs to be elucidated in controlled trials.

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