Observation as a Therapeutic Option for Head and Neck Lymphatic Malformations: A Survival Analysis of Spontaneous Regression

Juliana Bonilla-Velez

A thesis
submitted in partial fulfillment of the
requirements for the degree of

MASTER OF SCIENCE

University of Washington

2024

Committee:

Larry Kessler

Jonathan Perkins

Carrie Heike

Program Authorized to Offer Degree:

Health Systems and Population Health

University of Washington

Abstract

Observation as a Therapeutic Option for Head and Neck Lymphatic Malformations: A Survival Analysis of Spontaneous Regression

Juliana Bonilla-Velez

Chair of the Supervisory Committee:

Larry Kessler

Department of Health Systems and Population Health

Importance: Head and neck lymphatic malformations (HNLM) demonstrate significant variability in their natural history. While some malformations cause chronic severe functional impairment, others are asymptomatic and spontaneously regress. Understanding the frequency of spontaneous regression and the characteristics associated with regression will aid clinicians and families in making informed treatment choices and avoid unnecessary risks of intervention for a subset of patients.

Objective: To determine the incidence of spontaneous regression and identify factors associated with spontaneous regression.

Design: Non-concurrent prospective cohort study.

Setting: Single regional pediatric tertiary care academic center.

Participants: Patients with HNLM who were seen in the Vascular Anomalies Clinic and prospectively enrolled in an institutional quality improvement database between 2003 to 2022.

Exposure(s): Age of HNLM onset, primary location, distribution, cystic structure type, grade and De Serres staging.

Main Outcome and Measure(s): The incidence of complete spontaneous regression was estimated for the study population. A Kaplan-Meier curve was used to estimate the probability of spontaneous regression occurring over time. The two-sided log-rank test was used to test the association between exposure variables and survival. The effect of the exposures on the likelihood of developing spontaneous regression were assessed using Cox proportional hazards regression models.

Results: Of 368 patients with HNLM, 56% were male, and 55% were white. Most HNLMs were diagnosed prenatally or during the first year of life (53.5%), had a focal distribution (78.5%), were De Serres I or II (69%), and macrocystic (47.1%). Among the study population, 6.2% experienced complete spontaneous regression, at a median time of 23.3 months from HNLM onset. Factors significantly associated with complete spontaneous regression included cystic structure, HNLM distribution, primary location and De Serres staging ($p<0.05$).

Conclusions and Relevance: Macrocystic, localized HNLM are more likely to experience spontaneous regression. Future studies will examine interaction among these factors to better understand the drivers of regression. This work contributes to a deeper understanding of the natural history of HNLM that can directly inform clinical decision-making, decrease treatment risk, and optimize patient outcomes.

INTRODUCTION

Lymphatic malformations are the most common type of vascular malformation,[1] with an estimated incidence between 1.2 to 5 in 10,000 live births.[2-5] Most lymphatic malformations are located in the head and neck and exhibit considerable clinical heterogeneity.[6] While some children with head and neck lymphatic malformations (HNLM) present with an asymptomatic neck mass, others experience diffuse infiltration of the face, neck and aerodigestive structures resulting in significant morbidity such as dysphagia, respiratory failure requiring a tracheostomy tube, and stigmatizing facial differences,.[7,8] Historically, the most common interventions include invasive treatments with surgical resection and/or sclerotherapy.[9] In addition, the discovery that *PIK3CA* variants cause most HNLM has created opportunities to introduce novel pharmacologic treatment options.[8-10] [9,11-14] However, it is well-documented that a subset of patients will experience spontaneous regression of the HNLM, a process by which a HNLM progressively decreases in size (partial regression) and may resolve completely (complete regression).[8 ,15-17] Despite the fact that there are multiple treatment options available, there is scarcity of evidence to inform which treatments are likely to be most effective for a given patient.[9,11,18-20]

Outcome studies for common interventions have shown variable results. Surgical resection for patients with localized macrocystic HNLMs is associated with complete resolution in up to 90% of patients, and relatively few long-term complications have been reported.[21-23] However, surgery for more extensive malformations, particularly those associated with bilateral, microcystic, and/or mucosal involvement, have been associated with poorer outcomes and significantly more risk.[1,18,21,22,24] Sclerotherapy involves percutaneous administration of a sclerosing agent to the malformation.[11,20] Similarly to surgery, sclerotherapy is most successful in macrocystic LM, while results for microcystic disease are modest (53 to 89% for macrocystic vs. 35% for microcystic cure rates).[11,20] A retrospective cohort study of surgery vs. sclerotherapy showed similar effectiveness, defined as a need for further therapy within a year of the intervention.[9,25] The recent discovery that *PIK3CA* variants are detected in 75% of HNLM[26,27] and that LM occur through activation of the PI3K pathway has allowed for the development of medical therapies for HNLM. Medications inhibiting different levels of the pathway[28] include sirolimus,[14,29,30] aspirin,[31] miransertib,[32,33] and alpelisib.[34] Results from published studies of medical therapies for HNLM include a reduction in their size and associated symptoms but have not led to complete resolution of the malformations.[12,30,34]

For patients without significant functional impacts, observation can be an effective clinical strategy as it allows time for spontaneous regression to occur. Despite the significance of this known phenomenon, healthcare providers are hesitant to observe patients with HNLM, in part, because the process of spontaneous regression in HNLM is inadequately understood and we lack sufficient data to inform providers about those patients who are most likely to experience spontaneous regression. Retrospective studies among patients with LM have reported frequencies of regression ranging from 12% to 60%.[8,15-17,23] and the time from diagnosis to regression ranged from 2 months to 16 years[8,15-17,23] Macrocystic lesions and those located in the posterior or lateral neck are most likely to demonstrate spontaneous regression.[8,15-17,23] With our limited understanding of the process of spontaneous regression, our ability to make clinical recommendations for observation may be constrained. Improving our understanding of this process and identifying the predictors of spontaneous regression in HNLM would inform evidence-based clinical decision-making and protect patients from unnecessary and potentially harmful risks associated with interventions.

At our institution [Seattle Children's Hospital (SCH), Seattle, WA], we recommend observation to all patients with an HNLM unless they are experiencing functional compromise.[8] In our previous study comparing patients who underwent observation (only) to those who had invasive treatments, we saw that 58% of those in the observation group experienced spontaneous regression.[8] This study seeks to investigate the incidence, timing and likelihood of developing spontaneous regression among children with HNLM.

METHODS

We conducted a non-concurrent prospective cohort study. Our primary objectives were to (1) determine the incidence of spontaneous regression using a survival model; and (2) identify factors associated with spontaneous regression using Cox proportional hazard ratios. Approval for this study was obtained from the institutional review board (IRB; STUDY00003656).

Population

Patients with HNLM were identified from a single regional pediatric tertiary care academic center using our institutional vascular anomalies quality improvement database, in which patients were prospectively enrolled between 2003 to 2022. All patients aged birth to 21 years at the time of initial assessment who received a clinical diagnosis of HNLM by a member of the vascular anomalies team. Patients with <6 months of follow-up were excluded.

Data collection

We abstracted data from the electronic medical records on demographics, clinical information, invasive treatments (surgeries and sclerotherapies), and evidence of spontaneous regression. Clinical data were abstracted independently and masked to the outcome. Discrete data elements were imported from the SCH electronic data warehouse. Study team members manually abstracted data for variables identified in free text chart notes and surgical records. Data were stored in a REDCap® database.

Definitions of variables used in the analysis and the conceptual model

Date of onset was the date when the family reported the appearance of the malformation or the date of clinical diagnosis by a provider. HNLM sites were rated based on standard classification systems.[35,36] *HNLM distribution* was categorized as *focal* when it involved a single anatomic subsite, *regional* when the LM involved 1-3 anatomically adjacent subsites, or *generalized* when it involved more than 4 subsites.

The *observation period* corresponds to the amount of time each patient was observed and included the time from the date of onset to the date of complete regression, invasive treatment, or last follow up visit. The *time to partial* and to *complete spontaneous regression* were calculated from the *date of onset* until the first *date of partial regression* or the first *date of complete regression* as documented by a provider. Among patients who did not have an intervention, HNLM was considered *partially regressed* if it decreased in size but was still visible or *completely regressed* if there was no visible HNLM documented. Patients were observed until they were censored. *Censoring* occurred when (1) patients underwent surgical resection, laser ablation or received sclerotherapy, as these events would alter the natural history, (2) patients were lost to follow up or (3) patients reached 21 years of age. By using survival analysis methods, this study incorporated observed time among all patients regardless of treatment history in our analysis.

We developed a conceptual model for factors likely to be associated with spontaneous regression based on literature review and clinical experience (**Figure 1**). Such factors include neck location, limited extent, macrocystic composition, and <5 macrocysts.[8,15-17] We examined the following covariates: age at onset of HNLM, sex, race/ethnicity, HNLM sites , HNLM distribution (focal, regional, or generalized), De Serres staging (I-V),[7] grade (I, unilateral, II bilateral),[37] Wiegand staging (I to IV),[38] and cystic structure (macrocystic/>2 cm, mixed, or microcystic/<2 cm).

Analysis

We conducted the primary analysis on patients with >6 months of follow up to allow detection of change over time. A sensitivity analysis was performed with the entire cohort to assess the overall stability of the results. Continuous variables were presented as mean and standard deviation or median and interquartile range (IQR), as appropriate. Categorical variables were described as frequencies and percentages. Group level comparisons were made with Fisher's exact test to investigate the independence between two categorical variables. A Kaplan-Meier curve was used to estimate the probability of spontaneous regression occurring over time. The two-sided log-rank test was used to test the association between clinical characteristics and survival. The effect of covariates on the likelihood of developing spontaneous regression were assessed using Cox proportional hazards regression models to estimate hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs). For covariates without failure events in a sub-category, the Cox proportional hazards models were applied excluding the zero-event sub-category to avoid uninterpretable HRs and 95% CIs. Statistical significance was determined using a two-tailed p-value < 0.05. Statistical analyses were performed using R Statistical Software (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population

The population included 298 patients with HNLM, most of whom were male (58%), white (56%), and 72% of the population identified as Non-Hispanic. English was the preferred language of care (90%). Most participants had private (45%) or public (33%) insurance. Most patients resided in Washington state (80%) and in a metropolitan area (83%; **Table 1**).

The onset of HNLM occurred prenatally or at birth (46%), in the first 3 years (25%), between ages 3-6 years (11%), and after age 6 years (18%). The malformation was most frequently located in the lower face (40%) or neck (40%). HNLM was localized to a single area of the face or neck in most cases (63%), 26% were regional, and 10% had a more generalized distribution. HNLM De Serres staging was stage I (37%), stage II (40%), and stage III (10%), with only 10% and 3.4% being stage IV and V, respectively; corresponding to 80% being grade I and 13% grade II. Wiegand stage for HNLM involving the tongue (n=59) was 32% stage I and II, 9% stage III and 59% stage IV. Almost half of HNLM were macrocystic (43%; **Table 1**).

Patients had a median follow up of 57.6 months (IQR 15.8, 119.3). The median observation period for the cohort was 25 months (IQR 11.2, 63.4), while for patients who did not undergo invasive treatments was 42 months (IQR 17.1, 111.4), and for those who eventually did was 15.2 months (IQR 9.5, 33.5).

Complete Spontaneous Regression and Associated Factors

The incidence of complete spontaneous regression was 9.1% for the study population. Among patients who were observed and never required an invasive treatment, the incidence of complete regression was 19.7%. The median time from HNLM onset to demonstrating partial spontaneous regression is 10.5 months (IQR 5.5, 22.5), and 12 months to the development of complete spontaneous regression (IQR 6.68, 27.43).

Factors associated with complete spontaneous regression included location in the neck (81% vs. 37%, p=0.003); macrocystic structure (96% vs 4% microcystic and 0% mixed, p <0.001), focal distribution (88.5% vs. 11.5% regional, and 0% generalized, p =0.052), grade 1 (100% vs. 0% grade 2, p= 0.055) and De Serres I staging (73.1% vs. 15.4% II and 11.5% III, p <0.001). Spontaneous regression occurred in children of both genders, and across various ages, races, ethnicities, and ages of onset. Patients with HNLM located in the upper face, midface, or with generalized or bilateral distribution, nor with any mixed HNLM or with any Wiegand tongue staging developed complete spontaneous regression, and only one patient with a microcystic HNLM did (**Table 2**).

Survival Analysis of Spontaneous Regression

The probability of regression is greater among patients with malformations in the lower face and neck than xxxx? (p<0.0001). The likelihood of regression for patients with lesions in the neck is 5.6 times greater than for patients with malformations in the lower face (95%CI 2.08-14.9, p<0.001). The likelihood of regression is greater for macrocystic HNLM (p < 0.0001). Macrocystic HNLM have a 32.2 times greater likelihood of regression than patients with microcystic malformations (95%CI 4.29-241, p<0.001). The probability of regression over time based on De Serres staging is greater for HNLM that are stage I and II than xxxx? (p<0.001). Patients with grade I LM are more likely to develop complete regression than patients grade II (p=0.043). There was no statistically significant difference in the rates of complete regression based on patient age of onset (p=0.51), or LM distribution (p=0.1). Importantly, patients with HNLM that had microcystic or mixed cystic structure, were located in the face (scalp, skull base, forehead, orbit, midface, oral cavity, or parotid/parapharyngeal space), had a regional or generalized distribution, were De Serres IV/V or Grade II were highly unlikely to exhibit regression (n=0 or 1, p<0.05, **Table 2**, **Figure 2**). In our sensitivity analysis of 368 patients with a HNLM with any length of follow-up, there were no deviations from these findings.

DISCUSSION

Our study results showed an incidence of complete spontaneous regression of 9.1% among the study population and the time from HNLM onset to developing complete spontaneous regression was 12 months (IQR 5.5 to 22.5 months). Factors such as macrocystic structure, focal distribution, neck location, De Serres I staging, and being grade I significantly increase the likelihood of developing complete regression.. These findings are consistent with prior studies and underscore the importance of considering cystic structure and anatomical distribution in patient prognostication .
Sociodemographic characteristics are not associated with differential likelihood of

regression. Importantly, patients with HNLM involving the upper face or midface, with mixed or microcystic composition, and those with more extensive unilateral or bilateral involvement do not exhibit spontaneous regression.

Only four published studies have primarily focused on spontaneous regression of LM (**Table 3**). In a study by Perkins et al. of 104 patients with HNLM at 2 pediatric hospitals with ≥1 year follow-up (1999 to 2005), 12.5% showed complete spontaneous regression (n=13).[15] Patients with regressing LM had a bimodal age distribution (at birth, and 4.2 years (range 2-138 months), De Serres stage 1-3, had involvement of the posterior with or without part of the anterior neck (12/13 patients), all were macrocystic and one had >5 septae. A sub-analysis of 64 patients at SCH with imaging available (55 non-regressing vs. 9 regressing) showed that macrocystic LM (p=0.008), having <5 septae (p=0.00), and having limited extent (p=0.00) were associated with regression compared to non-regressing LM.[15] The mean time to regression was 4.5 months (range 2-7 months) and the average duration of follow up was 33.8 months (range 16-48 months). Authors conclude that regressing LM share certain characteristics and start showing regression within 7 months.

In 2017, Kato, et al[16] reported on 153 patients with LM of the head, neck, and extremities with ≥3 months of observation and ≥6 months of follow up after treatment in Japan over 34 years (1983-2016). Spontaneous regression was defined as a >20% decrease in size over 3 months and occurred in 77 patients (50%). Of these, 72 (94%) were macrocystic and 5 (6%) were mixed. Among 77 patients with regressing LM, 17 patients (22%) developed a recurrence (most with macrocystic LM) between 6m to 6y after the initial regression, and 3 patients had multiple recurrences. Seven patients with recurrence underwent additional treatments (sclerotherapy in 4, suction in 2, surgery in 1).

In 2021, Bonilla-Velez, et al[8] studied 191 patients managed under an active observation shared-decision making model where HNLM not causing functional compromise are offered active observation for 6–9 months, hypothesyzing that observation could be an effective therapeutic strategy. Spontaneous regression was defined as complete resolution. Of 65 patients in the observation group (34%), 36 experienced regression (58%). There were 126 patients who received invasive treatments. Factors associated with regression included macrocystic structure and neck location (p=0.003). Eight patients (12%) subsequently had invasive treatments. The authors conclude that active observation for patients without functional compromise appears to be safe and allows for regression to occur

Thorburn, et al [17] reported on patients with LM in any location managed between 1989–2019 in a Canadian pediatric hospital. Regression was defined as an improvement in the appearance of the lesion, categorized as partial or complete, per pediatric surgeon assessment at their follow up. Among 32 patients observed, 18 (56%) exhibited partial regression while 8 (25%) had complete regression and 6 (18%) did not regress. Average time to regression was 6.6 years. The authors advocate for observation as initial therapy for non-life-threatening LM.

In addition to these larger studies, spontaneous regression of LM has been noted in case series and case reports. Five case series on institutional treatment outcomes have reported cases of spontaneous regression (8/45 neck HNLM with complete regression,[39] 8/46 neck LM with complete regression,[1] of 11/46 observed HNLM, 5/11 had complete regression,[23] 2/177 body LM had partial regression,[40] and of 62/164 observed body LM, 16/62 had complete regression,[41]), as well as case reports for LM in the orbit,[42-44] parotid,[45,46] neck,[47,48] mediastinum,[49] and abdomen.[50-55]

Our results are consistent with the existing literature and demonstrate the potential for spontaneous regression when the HNLM is localized, macrocystic, and located in the neck. However, the wide variability in the composition of study populations, definitions for outcomes, and reported rates of regression among published studies makes comparisons challenging and warrants additional investigations to address critical remaining questions. How do we effectively counsel parents and patients regarding the likelihood of spontaneous regression in their child? Furthermore, there is often correlation among the variables associated with complete regression, such as macrocystic composition and neck localization, such that discerning what are the specific factors that are driving the process of regression remains elusive. Is regression primarily linked to being macrocystic and focal? or is there some intrinsic property in the neck that influences the likelihood of regression? Our study serves as an initial step in elucidating these complex associations by providing estimates of regression likelihood based on HNLM characteristics. Future studies that explore the relationships among predictors, consider potential confounding and interaction among these factors will allow for the identification of more specificpredictors of regression.

Our study advances our understanding of spontaneous regression in HNLM in several ways. It reports on the largest HNLM population with the longest follow up in the literature, enabling more robust statistical analyses. Our nonconcurrent retrospective cohort study design serves as a higher level of evidence than prior studies. We have conducted a systematic evaluation of the HNLM phenotype, as well as patient and clinical factors to have well-defined predictors and minimize missclassification. Implementing survival methods allows us to analyze the time all patients with a HNLM were observed up to when they had an invasive treatment or were lost to follow-up, which provides a better population-level understanding of the process of spontaneous regression and offers a different perspective from the existing literature that has focused on group-level comparisons. In addition, it provides estimates of the likelihood of regression based on HNLM characteristics. This approach also allowed us to clearly identify HNLM patients who will not regress, information that is equally relevant and previously unreported. Together, these contributions represent an advancement in our understanding of the process of spontaneous regression in HNLM.

While our study offers valuable insights into HNLM, several limitations warrant consideration. We relied on data from medical records in this retrospective study, which introduces inherent biases and limitations in data collection and analysis, such as selection bias and measurement error. To minimize misclassification, quality control was performed by an independent reviewer for key covariates and outcomes on >10% of patients. There is some selection bias from differential attrition, as patients with complete regression may elect to forego follow-up visits and thus the event would not be captured in the medical record, as well as patients with functional compromise may undergo invasive treatments shortly after diagnosis and thus regression cannot be seen. We have attempted to minimize these effects by including all the observed time among all patients in our survival analysis, but residual confounding remains. Additionally, the study population was drawn from a single regional pediatric tertiary care center. This regional subspecialty clinic provides care to children from a large 5-state region, and future multi-center collaborations will allow for evaluation of the generalizability of our findings to US and global populations with HNLM. There is some inherent bias related to individual providers, clinical circumstances and parental preferences that influence clinical decision making that are unable to be captured or controlled for and remain a limitation of any non-experimental study. Finally, our study is centered on pediatric care and thus we cannot comment on patients that present in adulthood. Future studies with larger, multicenter cohorts and prospective designs are warranted to address these limitations and further enhance our understanding of regression in HNLM.

In conclusion, we observed an incidence of complete spontaneous regression of 9.1% and the median time onset to complete spontaneous regression was 12 months. Factors such as macrocystic structure, focal distribution, neck location, grade 1 and De Serres I staging significantly increase the likelihood of developing complete regression.

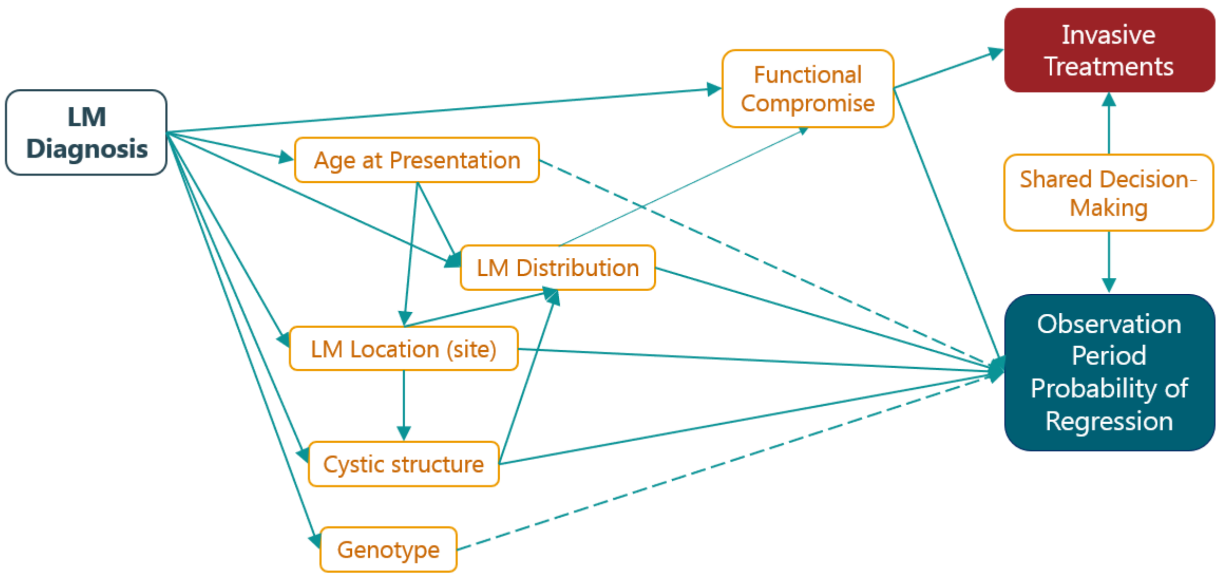
Patients with HNLM involving the upper face or midface, with mixed or microcystic composition, and those with more extensive unilateral or bilateral involvement do not exhibit spontaneous regression. Understanding the occurrence and predictors of spontaneous regression in HNLM is crucial for optimizing patient selection for treatments, minimizing unnecessary risks, and improving patient outcomes. Based on these findings and those of previous studies, we advocate for a one-year observation period for patients with HNLM that is macrocystic, of limited extent, and/or located in the neck, as non-intervention during this period may prove to be curative. Future work will assess the relationships among predictors, considering potential confounding and interaction effects to better predict patients likely to exhibit regression. This work contributes to a deeper understanding of the natural history of HNLM, informs clinical decision-making, decreases treatment risk, and enhances personalized treatment strategies to optimize patient outcomes.

Acknowledgements:

We extend our sincere gratitude to all who generously shared their expertise, time, and support toward the completion of this manuscript. Special thanks to Kiley Bijlani, Kristen Daniels, Angela Mills, Erik Stuhaug, and Eden Palmer for their exceptional contributions. Furthermore, we gratefully acknowledge the Seattle Children’s Research Institute for their support of this project through the Excellence in Research New Investigator Award.

Tables and Figures

Figure 1: Conceptual Model for Spontaneous Regression in Pediatric Head and Neck Lymphatic Malformations



Solid line: Reported association in the literature. Dotted line: Suspected association.

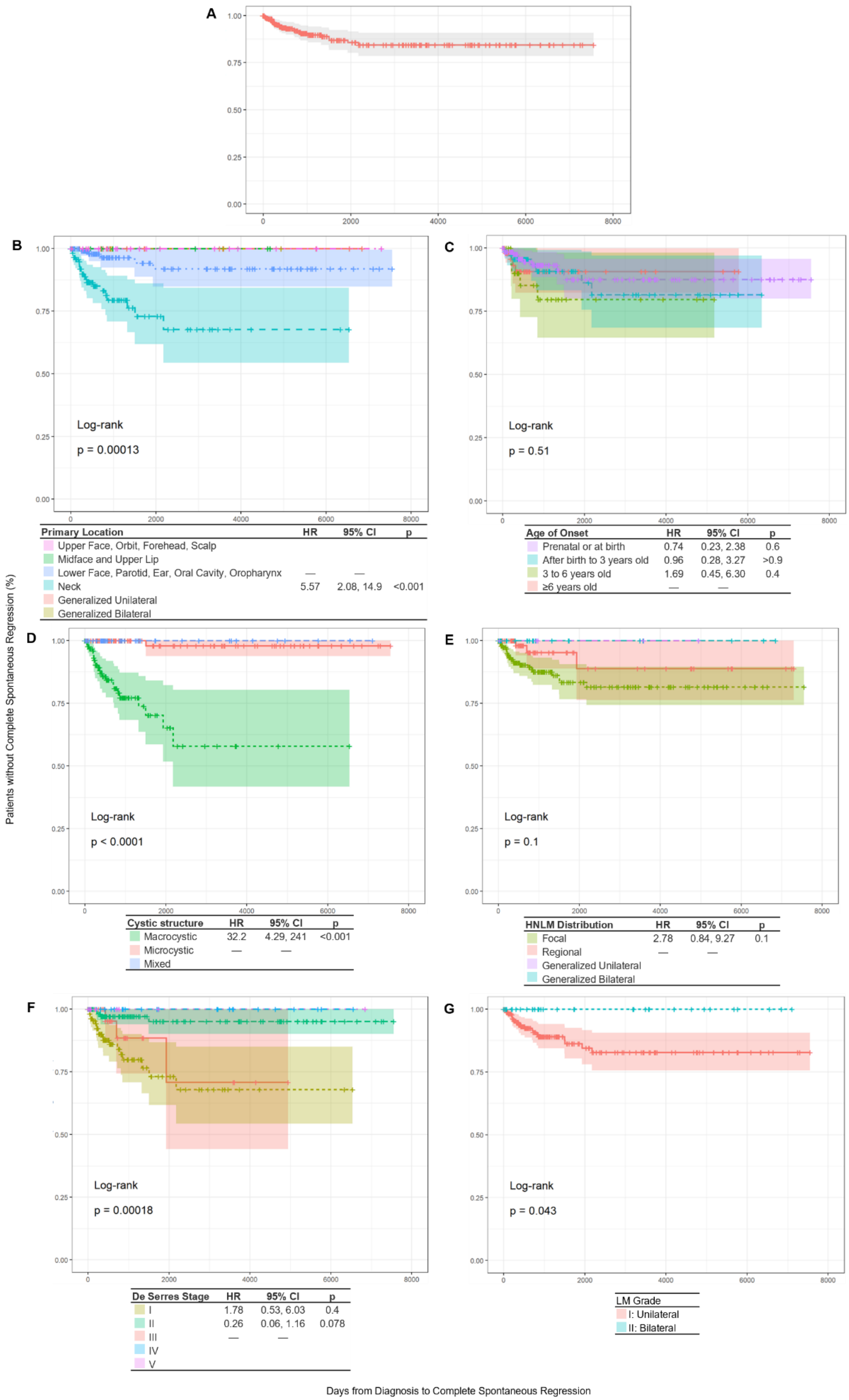

A
B
Log-rank
p = 0.00013
Primary Location HR 95% CI p
Upper Face, Orbit, Forehead, Scalp
Midface and Upper Lip
Lower Face, Parotid, Ear, Oral Cavity, Oropharynx — —
Neck 5.57 2.08, 14.9 <0.001
Generalized Unilateral
Generalized Bilateral
C
Log-rank
p = 0.51
Age of Onset HR 95% CI p
Prenatal or at birth 0.74 0.23, 2.38 0.6
After birth to 3 years old 0.96 0.28, 3.27 >0.9
3 to 6 years old 1.69 0.45, 6.30 0.4
≥6 years old — —
D
Log-rank
p < 0.0001
Cystic structure HR 95% CI p
Macrocystic 32.2 4.29, 241 <0.001
Microcystic — —
Mixed
E
Log-rank
p = 0.1
HNLM Distribution HR 95% CI p
Focal 2.78 0.84, 9.27 0.1
Regional — —
Generalized Unilateral
Generalized Bilateral
F
Log-rank
p = 0.00018
De Serres Stage HR 95% CI p
I 1.78 0.53, 6.03 0.4
II 0.26 0.06, 1.16 0.078
III — —
IV
V
G
Log-rank
p = 0.043
LM Grade
I: Unilateral
II: Bilateral
Patients without Complete Spontaneous Regression (%)
Days from Diagnosis to Complete Spontaneous Regression

Figure 2: Survival Analysis of Complete Spontaneous Regression in Head and Neck Lymphatic Malformations.

Kaplan-Meier Curves and Hazard Ratios for the Likelihood of Developing Complete Spontaneous Regression for (a) the overall cohort, and by (b) Primary Location, (c) Age of Onset, (d) Cystic Structure, (e) HNLM Distribution, and (f) De Serres Staging, and (g) LM Grade.

Abbreviations: HNLM = Head and Neck Lymphatic Malformations, HR = Hazard Ratio, CI = Confidence Interval.

Table 1: Demographic and Clinical Characteristics of the Study Population

Characteristics	N (%)
Age of Onset	
Prenatal or at Birth	137 (46.0)
After birth to 3 years old	73 (24.5)
3 to 6 years old	34 (11.4)
≥6 years old	53 (17.8)
Gender	
Female	125 (41.9)
Male	173 (58.1)
Race	
American Indian/Alaska Native	7 (2.3)
Asian	25 (8.4)
Black/African American	3 (1.0)
Native Hawaiian/Other Pacific Islander	1 (0.3)
White	167 (56.0)
Other, Multi-racial or Unknown	95 (31.9)
Hispanic/Latinx	
No	213 (71.5)
Yes	45 (15.1)
Unknown	40 (13.4)
Preferred language for care	
English	268 (89.9)
Spanish	22 (7.4)
Other language	8 (2.7)
Insurance Status	
Private	135 (45.3)
Medicare/Medicaid	97 (32.6)
Other government funding	12 (4.0)
Self pay/charity	34 (11.4)
Unknown	20 (6.7)
State of Residence	
WA	237 (79.5)
Other WWAMI	29 (11.0)
Other States	17 (6.5)
Unknown	15 (5.7)
Urban/rural status	
Metropolitan area	246 (82.6)
Micropolitan area (10,000-49,999)	23 (7.7)
Small town	12 (4.0)

Rural area	2 (0.7)
Unknown	15 (5.0)
Primary Location	
Upper Face, Orbit, Forehead, Scalp	19 (6.4)
Midface and Upper Lip	7 (2.3)
Lower Face, Parotid, Ear, Oral Cavity, Oropharynx	120 (40.3)
Neck	120 (40.3)
Generalized Unilateral	5 (1.7)
Generalized Bilateral	26 (8.7)
Unknown	1 (0.3)
Cystic structure	
Macrocystic	128 (43.0)
Microcystic	100 (33.6)
Mixed	43 (14.4)
Unknown	27 (9.1)
HNLM Distribution	
Focal	189 (63.4)
Regional	77 (25.8)
Generalized Unilateral	5 (1.7)
Generalized Bilateral	26 (8.7)
Unknown	1 (0.3)
LM Grade	
I: Unilateral	239 (80.2)
II: Bilateral	40 (13.4)
Unknown	19 (6.4)
De Serres stage	
I	110 (36.9)
II	118 (39.6)
III	29 (9.7)
IV	29 (9.7)
V	10 (3.4)
Unknown	2 (0.7)
Wiegand Staging for Tongue LM (n=52)	
I	16 (27.1)
II	3 (5.1)
III	5 (8.5)
IV	35 (59.3)
Unknown or Non-Tongue Involving (%N)	239 (80.2)

WWAMI, Washington, Wyoming, Alaska, Montana, and Idaho. NA, Non-applicable.
LM, Lymphatic Malformation.
*based on 2010 Rural-Urban Commuting Area (RUCA) Codes.

Table 2: Factors Associated with Spontaneous Regression

Characteristics	**Complete Regression**		
	No (n=271)	**Yes** (n=27)	**p***
Gender			
Female	114 (42.1)	11 (40.7)	1
Male	157 (57.9)	16 (59.3)	
Race			0.827
American Indian/Alaska Native	6 (2.4)	1 (4.0)	
Asian	24 (9.5)	1 (4.0)	
Black/African American	3 (1.2)	0 (0.0)	
Native Hawaiian/Other Pacific Islander	1 (0.4)	0 (0.0)	
White	152 (60.1)	15 (60.0)	
Other, Multi-racial or Unknown	67 (26.4)	8 (32.0)	
Hispanic/Latinx			0.775
No	194 (82.2)	19 (86.4)	
Yes	42 (17.8)	3 (13.6)	
Unknown			
Age of Onset			0.53
Prenatal or at Birth	127 (46.9)	10 (38.5)	
After birth to 3 years old	66 (24.4)	7 (26.9)	
3 to 6 years old	29 (10.7)	5 (19.2)	
≥6 years old	49 (18.1)	4 (15.4)	
Primary Location			0.003
Upper Face, Orbit, Forehead, Scalp	19 (7.0)	0 (0.0)	
Midface and Upper Lip	7 (2.6)	0 (0.0)	
Lower Face, Parotid, Ear, Oral Cavity, Oropharynx	115 (42.4)	5 (19.2)	
Neck	99 (36.5)	21 (80.8)	
Generalized Unilateral	5 (1.8)	0 (0.0)	
Generalized Bilateral	26 (9.6)	0 (0.0)	
Cystic structure			<0.001
Macrocystic	104 (42.3)	24 (96.0)	
Microcystic	99 (40.2)	1 (4.0)	
Mixed	43 (17.5)	0 (0.0)	
HNLM Distribution			0.052
Focal	166 (61.3)	23 (88.5)	
Regional	74 (27.3)	3 (11.5)	
Generalized Unilateral	5 (1.8)	0 (0.0)	
Generalized Bilateral	26 (9.6)	0 (0.0)	
LM Grade			0.055
I: Unilateral	216 (84.4)	23 (100.0)	

II: Bilateral	40 (15.6)	0 (0.0)	
De Serres stage			0.001
I	91 (33.7)	19 (73.1)	
II	114 (42.2)	4 (15.4)	
III	26 (9.6)	3 (11.5)	
IV	29 (10.7)	0 (0.0)	
V	10 (3.7)	0 (0.0)	
Wiegand Staging for Tongue LM			1
I	16 (27.1)	0 (0.0)	
II	3 (5.1)	0 (0.0)	
III	5 (8.5)	0 (0.0)	
IV	35 (59.3)	0 (0.0)	

* Fisher's exact test

Table 3: Studies Evaluating Spontaneous Regression in Lymphatic Malformations

Author	Year	Primary Research Question	Population, Setting, Study Period	Follow-up	Spontaneous Regression Definition	Onset of Regression	N	Spontaneous regression n (%)	Regression Associated Factors	Recurrence Post-Regression n/N (%), time	Level of Evidence*
Perkins, et al.	2008	Identifying clinical and radiographic characteristics associated with spontaneous regression	HNLM at 2 institutions (6y, 1999 to 2005). Compared regressing vs. non-regressing LM.	>1y Mean 33.8 m (Range 16-48)	LM resolution	<7 m	104	13 (12.5)	Macrocystic <5 septae Limited extent Posterior neck	N.R.	4
Kato, et al	2017	Characterization of the occurrence of spontaneous regression	Body LM (peripheral, not intraabdominal and/or intrathoracic) at 1 institution who did not undergo any treatment for 3 months (34y, 1983-2016).	>3m	>20% decrease in LM size over 3 months.	<3m per study design. N.R.	153	77	Macrocystic Older patients (~3y) Neck or axial	17/77 (22) 6m to 6y 7 additional tx	4
Bonilla-Velez, et al.	2021	Use of active observation as a treatment modality for HNLM without functional compromise	HNLM at 1 institution managed under an active observation model for >6-9 months (17y, 2000-2017).	>2y	LM resolution	N.R.	191 65 observed	36/191 (19) 36/65 (58)	Macrocystic Lateral Neck	N.R. 6 additional tx	4
Thorburn, et al	2022	Describe outcomes of conservative-based LM management using a population-based model with long-term follow up	Body LM at 1 institution without life-threatening symptoms (30y, 1989–2019)	Mean 6y (Range 1-19y)	Improvement appearance LM per assessment pediatric surgeon (partial or complete)	6.6y in observed group	39 32 observed	Among observed: Partial: 18/32 (56) Complete: 8/32 (25) Any: 26/32 (81) None: 6/32 (19)	N.R.	N.R.	4

Abbreviations: HNLM, Head and Neck Lymphatic Malformations, LM, Lymphatic Malformations, N.R. Not reported. Tx. Treatment.

References:

1. Kennedy TL, Whitaker M, Pellitteri P, Wood WE. Cystic hygroma/lymphangioma: a rational approach to management. *Laryngoscope*. Nov 2001;111(11 Pt 1):1929-37. doi:10.1097/00005537-200111000-00011
2. Filston HC. Hemangiomas, cystic hygromas, and teratomas of the head and neck. *Semin Pediatr Surg*. Aug 1994;3(3):147-59.
3. Harsha WJ, Perkins JA, Lewis CW, Manning SC. Pediatric admissions and procedures for lymphatic malformations in the United States: 1997 and 2000. *Lymphat Res Biol*. Summer 2005;3(2):58-65. doi:10.1089/lrb.2005.3.58
4. Longstreet B, Balakrishnan K, Saltzman B, Perkins JA, Dighe M. Prognostic value of a simplified anatomically based nomenclature for fetal nuchal lymphatic anomalies. *Otolaryngol Head Neck Surg*. Feb 2015;152(2):342-7. doi:10.1177/0194599814559190
5. Perkins JA. New Frontiers in Our Understanding of Lymphatic Malformations of the Head and Neck: Natural History and Basic Research. *Otolaryngol Clin North Am*. Feb 2018;51(1):147-158. doi:10.1016/j.otc.2017.09.002
6. Research Report: Comparative Effectiveness Review Methods: Clinical Heterogeneity. Content last reviewed November 2017. Effective Health Care Program, Agency for Healthcare Research and Quality, Rockville, MD. https://effectivehealthcare.ahrq.gov/products/clinical-heterogeneity-methods/research. Accessed 3/8/2024,
7. de Serres LM, Sie KC, Richardson MA. Lymphatic malformations of the head and neck. A proposal for staging. *Arch Otolaryngol Head Neck Surg*. May 1995;121(5):577-82.
8. Bonilla-Velez J, Whitlock KB, Ganti S, et al. Active Observation as an Alternative to Invasive Treatments for Pediatric Head and Neck Lymphatic Malformations. *Laryngoscope*. Jun 2021;131(6):1392-1397. doi:10.1002/lary.29180
9. Balakrishnan K, Menezes MD, Chen BS, Magit AE, Perkins JA. Primary surgery vs primary sclerotherapy for head and neck lymphatic malformations. *JAMA Otolaryngol Head Neck Surg*. Jan 2014;140(1):41-5. doi:10.1001/jamaoto.2013.5849
10. Bonilla-Velez J, Moore BP, Cleves MA, Buckmiller L, Richter GT. Surgical resection of macrocystic lymphatic malformations of the head and neck: Short and long-term outcomes. *Int J Pediatr Otorhinolaryngol*. Jul 2020;134:110013. doi:10.1016/j.ijporl.2020.110013
11. De Maria L, De Sanctis P, Balakrishnan K, Tollefson M, Brinjikji W. Sclerotherapy for lymphatic malformations of head and neck: Systematic review and meta-analysis. *J Vasc Surg Venous Lymphat Disord*. Jan 2020;8(1):154-164. doi:10.1016/j.jvsv.2019.09.007
12. Richardson CM, Perkins JN, Zenner K, et al. Primary targeted medical therapy for management of bilateral head and neck lymphatic malformations in infants. *Int J Pediatr Otorhinolaryngol*. Jan 2023;164:111371. doi:10.1016/j.ijporl.2022.111371
13. Padia R, Bly R, Bull C, Geddis AE, Perkins J. Medical Management of Vascular Anomalies. *Curr Treat Options Pediatr*. Jun 2018;4(2):221-236. doi:10.1007/s40746-018-0130-3
14. Wiegand S, Wichmann G, Dietz A. Treatment of Lymphatic Malformations with the mTOR Inhibitor Sirolimus: A Systematic Review. *Lymphat Res Biol*. Aug 2018;16(4):330-339. doi:10.1089/lrb.2017.0062
15. Perkins JA, Maniglia C, Magit A, Sidhu M, Manning SC, Chen EY. Clinical and radiographic findings in children with spontaneous lymphatic malformation regression. *Otolaryngol Head Neck Surg*. Jun 2008;138(6):772-7. doi:10.1016/j.otohns.2008.02.016
16. Kato M, Watanabe S, Kato R, Kawashima H, Iida T, Watanabe A. Spontaneous Regression of Lymphangiomas in a Single Center Over 34 Years. *Plast Reconstr Surg Glob Open*. Sep 2017;5(9):e1501. doi:10.1097/GOX.0000000000001501
17. Thorburn C, Price D. Expectant management of pediatric lymphatic malformations: A 30-year chart review. *J Pediatr Surg*. May 2022;57(5):883-887. doi:10.1016/j.jpedsurg.2021.12.053

18. Adams MT, Saltzman B, Perkins JA. Head and neck lymphatic malformation treatment: a systematic review. *Otolaryngol Head Neck Surg*. Oct 2012;147(4):627-39. doi:10.1177/0194599812453552
19. Balakrishnan K, Bauman N, Chun RH, et al. Standardized outcome and reporting measures in pediatric head and neck lymphatic malformations. *Otolaryngol Head Neck Surg*. May 2015;152(5):948-53. doi:10.1177/0194599815577602
20. Fernandes S, Yeung P, Heran M, Courtemanche D, Chadha N, Baird R. Sclerosing agents in the management of lymphatic malformations in children: A systematic review. *J Pediatr Surg*. May 2022;57(5):888-896. doi:10.1016/j.jpedsurg.2021.12.056
21. Bonilla-Velez J, Moore BP, Cleves MA, Richter GT. Surgical Resection of Macrocystic Lymphatic Malformations of the Head and Neck: Short and Long-Term Outcomes. *Int J Pediatr Otorhinolaryngol*. Mar 20 2020;134:110013doi: 10.1016/j.ijporl.2020.110013
22. Bajaj Y, Hewitt R, Ifeacho S, Hartley BE. Surgical excision as primary treatment modality for extensive cervicofacial lymphatic malformations in children. *Int J Pediatr Otorhinolaryngol*. May 2011;75(5):673-7. doi:10.1016/j.ijporl.2011.02.009
23. Gilony D, Schwartz M, Shpitzer T, Feinmesser R, Kornreich L, Raveh E. Treatment of lymphatic malformations: a more conservative approach. *J Pediatr Surg*. Oct 2012;47(10):1837-42. doi:10.1016/j.jpedsurg.2012.06.005
24. Raveh E, de Jong AL, Taylor GP, Forte V. Prognostic factors in the treatment of lymphatic malformations. *Arch Otolaryngol Head Neck Surg*. Oct 1997;123(10):1061-5. doi:10.1001/archotol.1997.01900100035004
25. Wittekindt C, Michel O, Streppel M, et al. Lymphatic malformations of the head and neck: Introduction of a disease score for children, Cologne Disease Score (CDS). Article. *Int J Pediatr Otorhinolaryngol*. Jul 2006;70(7):1205-1212. doi:10.1016/j.ijporl.2005.12.013
26. Luks VL, Kamitaki N, Vivero MP, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. *J Pediatr*. Apr 2015;166(4):1048-54 e1-5. doi:10.1016/j.jpeds.2014.12.069
27. Zenner K, Cheng CV, Jensen DM, et al. Genotype correlates with clinical severity in PIK3CA-associated lymphatic malformations. *JCI Insight*. Nov 1 2019;4(21)doi:10.1172/jci.insight.129884
28. Canaud G, Hammill AM, Adams D, Vikkula M, Keppler-Noreuil KM. A review of mechanisms of disease across PIK3CA-related disorders with vascular manifestations. *Orphanet J Rare Dis*. Jul 8 2021;16(1):306. doi:10.1186/s13023-021-01929-8
29. Alemi AS, Rosbe KW, Chan DK, Meyer AK. Airway response to sirolimus therapy for the treatment of complex pediatric lymphatic malformations. Article. *Int J Pediatr Otorhinolaryngol*. Dec 2015;79(12):2466-2469. doi:10.1016/j.ijporl.2015.10.031
30. Strychowsky JE, Rahbar R, O'Hare MJ, Irace AL, Padua H, Trenor CC, 3rd. Sirolimus as treatment for 19 patients with refractory cervicofacial lymphatic malformation. *Laryngoscope*. Jan 2018;128(1):269-276. doi:10.1002/lary.26780
31. Bonilla-Velez J, Whitlock KB, Ganti S, et al. Acetylsalicylic acid suppression of the PI3K pathway as a novel medical therapy for head and neck lymphatic malformations. *Int J Pediatr Otorhinolaryngol*. Dec 2021;151:110869. doi:10.1016/j.ijporl.2021.110869
32. Yu Y, Savage RE, Eathiraj S, et al. Targeting AKT1-E17K and the PI3K/AKT Pathway with an Allosteric AKT Inhibitor, ARQ 092. *PLoS ONE*. 2015;10(10):e0140479. doi:10.1371/journal.pone.0140479
33. Forde K, Resta N, Ranieri C, et al. Clinical experience with the AKT1 inhibitor miransertib in two children with PIK3CA-related overgrowth syndrome. *Orphanet J Rare Dis*. Feb 27 2021;16(1):109. doi:10.1186/s13023-021-01745-0
34. Wenger TL, Ganti S, Bull C, et al. Alpelisib for the treatment of PIK3CA-related head and neck lymphatic malformations and overgrowth. *Genet Med*. Nov 2022;24(11):2318-2328. doi:10.1016/j.gim.2022.07.026

35. Deschler DG, Moore MG, Smith RV. *Quick Reference Guide to TNM Staging of Head and Neck Cancer and Neck Dissection Classification*. 4 ed. American Academy of Otolaryngology–Head and Neck
Surgery Foundation; 2014.
36. Amin MB, American Joint Committee on Cancer., American Cancer Society. *AJCC cancer staging manual*. Eight edition / editor-in-chief, Mahul B. Amin, MD, FCAP ; editors, Stephen B. Edge, MD, FACS and 16 others ; Donna M. Gress, RHIT, CTR - Technical editor ; Laura R. Meyer, CAPM - Managing editor. ed. American Joint Committee on Cancer, Springer; 2017:xvii, 1024 pages.
37. Bonilla-Velez J, Whitlock KB, Ganti S, et al. Delaying Invasive Treatment in Unilateral Head and Neck Lymphatic Malformation Improves Outcomes. *Laryngoscope*. Apr 2023;133(4):956-962. doi:10.1002/lary.30237
38. Wiegand S, Eivazi B, Zimmermann AP, et al. Microcystic lymphatic malformations of the tongue: diagnosis, classification, and treatment. Article. *Arch Otolaryngol Head Neck Surg*. Oct 2009;135(10):976-83. doi:10.1001/archoto.2009.131
39. Broomhead IW. Cystic Hygroma of the Neck. *Br J Plast Surg*. Jul 1964;17:225-44. doi:10.1016/s0007-1226(64)80039-4
40. Saijo M, Munro IR, Mancer K. Lymphangioma. A long-term follow-up study. *Plast Reconstr Surg*. Dec 1975;56(6):642-51. doi:10.1097/00006534-197512000-00005
41. Hyvonen H, Salminen P, Kyrklund K. Long-term outcomes of lymphatic malformations in children: An 11-year experience from a tertiary referral center. *J Pediatr Surg*. Dec 2022;57(12):1005-1010. doi:10.1016/j.jpedsurg.2022.07.024
42. Yoshii M, Okisaka S, Nawashiro H, Tokumaru AM, Takahashi J. A case of orbital lymphangioma showing considerable shrinkage after limiting dissection. *Acta Ophthalmol Scand*. Apr 2004;82(2):242-3. doi:10.1111/j.1600-0420.2004.00150c.x
43. Mestak O, Mestak J, Pokorna K, Bruna J, Sukop A. Unusual regression of severe recurrent lymphatic malformation of a face after contraception and pregnancy. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology*. Oct 2012;28(10):764-6. doi:10.3109/09513590.2012.664190
44. Dhir SP, Jain IS, Dutta BN. Orbital lymphangioma (regression with corticosteroids). *Indian J Ophthalmol*. Apr 1976;24(1):36-8.
45. Vasconcelos BN, Benez MD, Bressan AL, Oliveira EF. Involution of a cystic hygroma of the face following local infection. *An Bras Dermatol*. Jan-Feb 2011;86(1):135-7. doi:10.1590/s0365-05962011000100020
46. Kumar N, Kohli M, Pandey S, Tulsi SP. Cystic hygroma. *Natl J Maxillofac Surg*. Jan 2010;1(1):81-5. doi:10.4103/0975-5950.69152
47. Xavier C, Emil S. Spontaneous resolution of lymphatic and venous malformations. *Eur J Pediatr Surg*. Sep 2010;20(5):342-5. doi:10.1055/s-0029-1243632
48. Diaz Rodriguez D, Benitez Del Rosario JJ, Valido Quintana M, Sanchez Tudela AT. Spontaneous regression of a cervical giant cystic lymphangioma. *Acta Otorrinolaringol Esp (Engl Ed)*. May-Jun 2021;72(3):195-197. Regresion espontanea de linfangioma quistico cervical gigante. doi:10.1016/j.otorri.2019.11.009
49. Ogawa-Ochiai K, Sekiya N, Kasahara Y, et al. A case of mediastinal lymphangioma successfully treated with Kampo medicine. *J Altern Complement Med*. Jun 2011;17(6):563-5. doi:10.1089/acm.2010.0562
50. Chiappinelli A, Forgues D, Galifer RB. Congenital abdominal cystic lymphangiomas: what is the correct management? *J Matern Fetal Neonatal Med*. Jul 2012;25(7):915-9. doi:10.3109/14767058.2011.600364
51. Amodeo I, Cavallaro G, Raffaeli G, et al. Abdominal cystic lymphangioma in a term newborn: A case report and update of new treatments. *Medicine (Baltimore)*. Feb 2017;96(8):e5984. doi:10.1097/MD.0000000000005984

52. Tan DTM, Chok AY, Farah BL, Yan YY, Toh EL. Spontaneous partial regression of a microcystic jejunal mesenteric lymphangioma and a proposed management algorithm. *BMJ Case Rep*. Nov 24 2019;12(11)doi:10.1136/bcr-2019-231037

53. Maranna H, Bains L, Lal P, et al. Cystic Lymphangioma of the Greater Omentum: A Case of Partial Spontaneous Regression and Review of the Literature. *Case Rep Surg*. 2020;2020:8932017. doi:10.1155/2020/8932017

54. Lee JM, Chung WC, Lee KM, et al. Spontaneous resolution of multiple lymphangiomas of the colon: a case report. *World J Gastroenterol*. Mar 21 2011;17(11):1515-8. doi:10.3748/wjg.v17.i11.1515

55. Joo SH, Kim MJ, Kim KW, Lee WJ, Park MS, Lim JS. Spontaneous regression of a cystic tumor in a postpartum woman; is it a cystic lymphangioma? *Yonsei Med J*. Aug 31 2007;48(4):715-8. doi:10.3349/ymj.2007.48.4.715