SYSTEMATIC REVIEW

blood advances

Significance of E-lesions in Hodgkin lymphoma and the creation of a new consensus definition: a report from SEARCH

Eline A. M. Zijtregtop,[1,*] Jamie Zeal,[2,3,*] Monika L. Metzger,[2,4] Kara M. Kelly,[5] Christine Mauz-Koerholz,[6,7] Stephan D. Voss,[8] Kathleen McCarten,[9] Jamie E. Flerlage,[2,4,†] and Auke Beishuizen[1,10,†]

[1]Department of Pediatric Oncology/Hematology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; [2]Department of Pediatrics and [3]Department of Medicine, University of Tennessee Health Sciences Center, Memphis, TN; [4]Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN; [5]Department of Pediatrics, Roswell Park Comprehensive Cancer Center, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY; [6]Department of Pädiatrische Hämatologie und Onkologie, Zentrum für Kinderheilkunde der Justus-Liebig-Universität Giessen, Giessen, Germany; [7]Medical Faculty, Martin-Luther-University of Halle-Wittenberg, Halle, Germany; [8]Department of Radiology, Boston Children's Hospital Dana-Farber Cancer Institute, Boston, MA; [9]Imaging and Radiation Oncology Core-Rhode Island, Lincoln, RI; and [10]Department of Hemato-Oncology, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

The International Staging Evaluation and Response Criteria Harmonization for Childhood, Adolescent, and Young Adult Hodgkin Lymphoma (SEARCH for CAYAHL) seeks to provide an appropriate, universal differentiation between E-lesions and stage IV extranodal disease in Hodgkin lymphoma (HL). A literature search was performed through the PubMed and Google Scholar databases using the terms "Hodgkin disease," and "extranodal," "extralymphatic," "E lesions," "E stage," or "E disease." Publications were reviewed for the number of participants; median age and age range; diagnostic modalities used for staging; and the definition, incidence, and prognostic significance of E-lesions. Thirty-six articles describing 12 640 patients met the inclusion criteria. Most articles reported staging per the Ann Arbor (72%, 26/36) or Cotswolds modification of the Ann Arbor staging criteria (25%, 9/36), and articles rarely defined E-lesions or disambiguated "extranodal disease." The overall incidence of E-lesions for patients with stage I-III HL was 11.5% (1330/11 602 unique patients). Available stage-specific incidence analysis of 3888 patients showed a similar incidence of E-lesions in stage II (21.2%) and stage III (21.9%), with E-lesions rarely seen with stage I disease (1.1%). E-lesions likely remain predictive, but we cannot unequivocally conclude that identifying E-lesions in HL imparts prognostic value in the modern era of the more selective use of targeted radiation therapy. A harmonized E-lesion definition was reached based on the available evidence and the consensus of the SEARCH working group. We recommend that this definition of E-lesion be applied in future clinical trials with explicit reporting to confirm the prognostic value of E-lesions.

Introduction

Hodgkin lymphoma (HL) is a relatively rare cancer with excellent cure rates; but because of differences in staging criteria and risk stratification, outcomes cannot be directly compared between clinical trials.[1-6] HL primarily affects the lymph nodes and the spleen but extranodal involvement does occur. The 1965

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*E.A.M.Z. and J.Z. are joint first authors.

†J.E.F. and A.B. are joint senior authors.

Rye Classification stated that involvement of the bone marrow, lung parenchyma, pleura, liver, bone, skin, kidneys, gastrointestinal tract, or any tissue outside of the lymphatic system was considered stage IV disease.[7] Musshoff[8] first noted that extralymphatic disease contiguous with a region of lymphatic involvement treated with intensive radiotherapy alone does not have the same poor prognostic implication as widespread extralymphatic disease; he divided the existing Rye Classification group IV into stage IV per continuitatem and stage IV per disseminationem.[8] This led to proposals of the subclassification of "EN"[8] or subscript "E"[9] for extralymphatic disease within stages I, II, and III HL; "E-lesions" were initially defined as proximal or contiguous extranodal extensions that did not require modification of the nodal irradiation field or dose and did not have negative prognostic implications.[10] These findings were incorporated into a new classification system[9] and disease staging procedures[11] defined at the Ann Arbor meeting in 1971 that were rapidly and widely adopted for adult and pediatric HL.[10]

Over time, this definition has continued to be modified and studied. In 1982, Yarnold showed that disease that is contiguous but too large to meet this radiotherapy definition, is associated with a poor prognosis (possibly worse than other stage IV without this feature).[12] In 1984, the complexity of staging E-lesions was demonstrated when 14 internationally recognized HL centers disagreed on the classification (E-lesion vs stage IV) of 4 representative cases of nearby but not contiguous extranodal disease of the lung or bone; 2 cases were complete stalemates.[13] The subsequent 1989 Cotswolds modification of the Ann Arbor staging system incorporated success with chemotherapy in early unfavorable disease, improved imaging diagnostics (computed tomography [CT] and magnetic resonance imaging [MRI]), and prognostic advancements (bulk disease and number of involved nodal sites as risk factors); the E-lesion definition was retained with different examples of local extralymphatic organ involvement provided.[10]

In 2011, a dramatic change for adult HL staging was made in Lugano, Switzerland in response to outcomes with the widespread use of chemotherapy and combined modality therapy (CMT).[14] This update deemed "E" subclassification no longer clinically relevant for advanced-stage disease (stages IIx, III, and IV); the "E" distinction remains meaningful in cases of limited extranodal disease in the absence of nodal involvement (stage IE) or for patients with stage II disease and direct extension to a nonnodal site (stage IIE).[14] Notably, these modifications have not been applied to the pediatric population.

Agreement regarding E-lesions vs disseminated extranodal disease is challenging and yet essential for both individual patients and the interpretation of clinical trials. Central imaging reviews for large cooperative group studies have shown that discrepancies in the identification of E-lesions affect both the stage and potential treatment for individual patients.[15,16] Further emphasizing the importance of appropriate identification of E-lesions, the presence of extranodal disease is used as a poor prognostic criterion to identify unfavorable early-stage disease by the adult German Hodgkin Study Group (GHSG)[17,18] and in the determination of treatment groups in the EuroNet Pediatric Hodgkin Lymphoma (PHL) C1 and C2 trials.[19,20] Inappropriate patient risk assignment may lead to inappropriate conclusions drawn about the effectiveness of a given treatment regimen. The distinction between patients with local (E-lesions) or disseminated (stage IV) extranodal HL is often unclear in the literature, making it challenging to determine the prognostic value of either group.

The International Staging Evaluation and Response Criteria Harmonization for Childhood, Adolescent, and Young Adult HL (SEARCH for CAYAHL) initiative provides a platform for global collaboration to improve the cure rates of children with HL by achieving consensus between consortia.[21] As part of this effort, we conducted a systematic review of the literature on the reporting of E-lesions in patients with HL. Here, we propose a universally acceptable and harmonized definition for E-lesions in pediatric patients with HL.

Methods

Search strategy

A systematic literature search was performed through the PubMed and Google Scholar databases for articles on E-lesions in patients with HL for articles published from 1 January 1960 to 1 August 2022 by using the combination of free-text keywords: "Hodgkin disease" [MeSH] AND (extranodal OR extralymphatic OR "E lesions" OR "E stage" OR "E disease"; Figure 1). Two authors (E.A.M.Z. and A.B.) independently screened each abstract per screening criteria for articles published from January 1960 to December 2016; if no exclusion criteria were met, the full manuscript was retrieved and reviewed. Reasons for exclusion were recorded. Reference lists were reviewed for additional candidate papers. A third author (J.Z.) repeated this process using the same search terms to screen articles published from 1 January 2017 to 1 August 2022. Although they did not meet the search criteria, several additional contemporary landmark trials (EuroNet PHL-C1, Hodgkin Lymphoma High Risk protocol 13, and GHSG Hodgkin's disease [HD]17) were also reviewed for inclusion. The date of the last database search was 6 September 2022. The manuscript was amended to add 1 significant recent publication that was published while this manuscript was under review. A fourth author (J.E.F.) reviewed articles as needed to determine appropriateness of inclusion or clarify interpretation.

Inclusion and exclusion criteria

Articles met criteria for inclusion if they offered information on the incidence or prognostic significance of E-lesions in HL and gave an explicit definition of E-lesions or reference staging per the Ann Arbor classification, the Cotswold modification, or Lugano criteria, or treatment protocols with E-lesion definitions. Acceptable examples of staging classifications and the latest international treatment protocols are listed in Tables 1-2.[19,20] We included articles without explicit definitions of extranodal involvement if they were limited to stages I-III, as the term "extranodal" could not be referring to stage IV disease in these patients. All patient ages were included, because many articles combined both pediatric and adult patients.

Articles were excluded if they were case reports or written in languages other than English, or if the study population did not include frontline classical HL (ie, nodular lymphocyte predominant HL, only relapsed or refractory HL, or patients with HIV or other immune disorders). We also excluded articles with unclear or incomplete definitions of extranodal or extralymphatic involvement. This encompassed the exclusion of articles that did not distinguish between E-lesions and stage IV extranodal involvement in their descriptive tables or analyses.

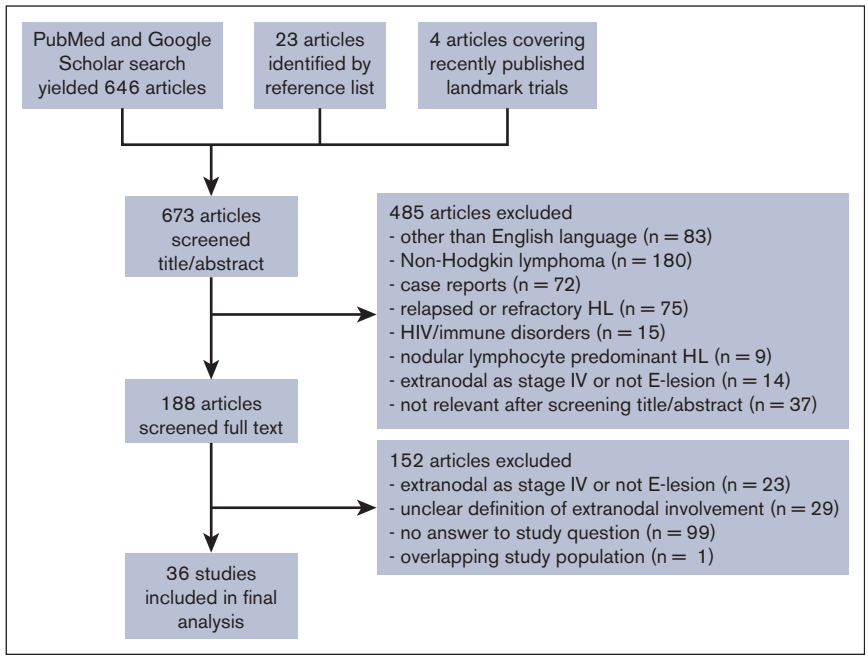

Figure 1. Flowchart of literature search. Diagram representing information flow in the review of literature describing E-lesions in studies of patients with Hodgkin lymphoma.

Outcomes

Two authors (E.A.M.Z. and A.B.) independently extracted data from identified articles published from January 1960 through December 2016; a third author (J.Z.) extracted data from articles published from 1 January 2017 through 1 August 2022. The following data were extracted from each article and recorded in a spreadsheet: the number of participants, median age and age range of participants at diagnosis, type of diagnostic tool(s) used for staging, the incidence of E-lesions, treatment, and the prognostic value of E-lesions. One author (J.Z.) manually verified all extracted data on a

Table 1. Definitions of E-lesions in different classification systems

Year	Classification	Reference	Definition of E-lesions
1966	Rye classification	7	E-lesions undefined
			Involvement of tissue outside of the lymphatic system considered stage IV disease
1971	Ann Arbor classification	9	Stage IE: a single extralymphatic organ or site
			Stage IIE: localized involvement of extralymphatic organ or site and ≥1 lymph node regions on 1 side of the diaphragm
			Stage IIIE: involvement of lymph node regions on both sides of the diaphragm with localized involvement of extralymphatic organ or site
			Examples: multiple nodules in the lung limited to 1 lobe or perihilar extension associated with ipsilateral hilar adenopathy; unilateral pleural effusion with or without lung involvement but with hilar adenopathy
			Liver involvement is considered stage IV/diffuse disease
1989	Cotswolds modification of Ann Arbor classification	10	Involvement of extralymphatic tissue on 1 side of the diaphragm by limited direct extension from an adjacent nodal site (ie, extranodal extension) with implicit expectation of prognosis equivalent to that for treatment of nodal disease of same anatomical extent
			May also include a discrete single extranodal deposit consistent with extension from a regionally involved node
			A single extralymphatic site as the only site of disease should be classified as stage IE; multiple extranodal deposits not included
			Anterior extension of a mediastinal mass into the sternum or chest wall or extension to lung or pericardium should be recorded as extranodal extension
			Extensive extranodal disease is designated stage IV
2011	ICML staging Lugano criteria	14	Stage IE: single extranodal lesion without nodal involvement
			Stage IIE: stage I or II by nodal extent with limited contiguous extranodal involvement
			Stage IIx, stage III, and stage IV: not applicable

ICML, International Conference on Malignant Melanoma.

Table 2. Definitions of E-lesions in recent pediatric treatment protocols

Protocol(s)	Reference	Definition of E-lesions
EuroNet PHL C1	19	Extralymphatic structures or organs that are infiltrated per continuum out of a lymphatic mass are termed E-lesion (eg, lung, intestine, and bones) and do not automatically qualify for stage IV. Exceptions: liver or bone marrow involvement always implies stage IV
		Pleura and pericardium: pleura and/or pericardial involvement are generally considered E-lesions. Involvement of the pleura is assumed if: the lymphoma is contiguous with the pleura without fat lamella, the lymphoma invades the chest wall, or a pleural effusion occurs, which cannot be explained by a venous congestion. Pericardial involvement is assumed if: the lymphoma has a broad area of close contact toward the heart surface beyond the valve level (ventriculus area), or a pericardial effusion occurs
		Lung: a disseminated lung involvement (implying stage IV) is assumed if there are >3 foci or an intrapulmonary focus has a diameter of >10 mm. E-lesion of the lung is restricted to 1 pulmonary lobe or perihilar extension with homolateral hilar lymphadenopathy
		Spleen: exclusive splenic involvement without other lymphatic disease is classified as stage I. Mere enlargement of liver/spleen only is not considered as involvement. Focal changes in the liver/ spleen structure that are tumor suspicious in ultrasonography are considered involved, independent of the FDG-PET result
EuroNet PHL C2	20	An E-lesion is a contiguous infiltration of a lymph node mass into extralymphatic structures or organs (eg, lung or bone). Disseminated organ involvement always implies stage IV.
		Pleural effusion is not considered to be an E-lesion. Involvement of the pleura is assumed if an adjacent nodal lesion infiltrates the pleura or chest wall AND the infiltrate and/or the adjacent nodal lesion is PET positive.
		Pericardial effusion is not considered to be an E-lesion. Pericardial involvement is assumed if an adjacent nodal lesion infiltrates the pericardium AND the infiltrate and/or the adjacent nodal lesion is PET positive.
		Lung: disseminated lung involvement is assumed if there are >2 small foci between 2 mm and 10 mm within the whole lung, or there is at least 1 intrapulmonary focus with a diameter of ≥10 mm
COG AHOD0031 & AHOD1331	Clinical trial*	Extralymphatic structures contiguous with sites of lymph node involvement are considered E-lesions (particularly lung). Pleural, pericardial, or chest wall infiltration by an adjacent nodal lesion, that is, PET positive would be considered an E-lesion. Liver and/or bone marrow involvement is not considered an E-lesion but rather considered stage IV. Pleural and pericardial effusions alone are not considered E-lesions.
		Stage IE: localized involvement of a single extralymphatic organ or site
		Stage IIE: localized contiguous involvement of a single extralymphatic organ or site and its regional lymph node(s) with involvement of ≥1 lymph node regions on the same side of the diaphragm
		Stage IIIE: involvement of lymph node regions on both sides of the diaphragm accompanied by localized contiguous involvement of an extralymphatic organ or site
		Stage IV: disseminated (multifocal) involvement of ≥1 extralymphatic organs or tissues, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement

COG, Children's Oncology Group; FDG, fluorodeoxyglucose.
*AHOD0031 clinicaltrials.gov identifier: NCT00025259; AHOD1331 clinicaltrials.gov identifier: NCT02166463. EuroNet-PHL-C1 clinicaltrials.gov identifier: NCT00433459. EuroNet-PHL-C2 clinicaltrial.gov identifier: NCT02684708.

second occasion. Overall and stage-specific incidences of E-lesions were calculated. Pairs of articles with overlapping patient populations were individually considered for inclusion in incidence calculations; attempts were made to maximize sample size and minimize double counting. Incidence calculations were repeated without articles that used risk-based inclusion criteria (with exception of disease stage) to evaluate for selection bias.

Results

Study selection

Our literature search produced 646 unique articles; 23 additional articles were identified within the reference lists of these publications, and 4 articles reporting on contemporary landmark trials were also reviewed. After screening the abstracts, 485 were excluded per our screening criteria. We reviewed 188 full-text articles and excluded an additional 152 publications (Figure 1). In total, 36 articles were included in our final incidence analysis (Table 3). Several articles contained overlapping patient populations. If the articles provided meaningfully distinct incidence and/or prognostic information, they were both included and collated under the same study number.

The first 2 articles with overlapping populations were by Levi et al[22] and Wiernik and Slawson.[23] Wiernik and Slawson reported a follow-up of the patient population described by Levi et al and also added unique patients to the group. The only stage-specific E-lesion incidence data available was from the Levi et al study. To avoid double counting patients, only the larger population reported by Wiernik was used for the overall incidence calculation. Both articles were used in the prognosis analysis because they provided unique outcomes analyses. Another article by Levi[24] was excluded because it did not include unique E-lesion incidence or prognostic data.

A second instance of overlapping populations was encountered when Hoppe[25] and Crnkovich[26] described Stanford HL outcomes

Table 3. Summary of studies included in incidence analysis

Study	Year	Author	Reference	Study period	n*	Median age, y (range)	Staging criteria	E-Lesion location (n)	Staging tools	Incidence of E-lesions by stage			Treatment (E/total, % with E-lesion)	Impact of E-lesions on prognosis, notable covariates
										I	II	III		
1	1977	Mill et al	55	1968-1972	116	nd	Ann Arbor	nd	CXR w/wo chest tomog, IVP, L/S, LAG, BMBx, lap (58%).	IA: 0% (0/23)	IIA: 4% (2/51)	IIIA: 4% (1/24)	RT (IFRT, EFRT, TNI) vs CMT	There were more relapses in E-lesion group (statistical significance, nd).
										IB: 0% (0/2)	IIB: 19% (3/16)	na		
2	1977	Levi et al	22†	1968-1976	111	(9-60)	Ann Arbor	Lung only (12), lung + other (2), thyroid (2), and subcutaneous (1)	CXR w/wo chest tomog (4%); EBx (8); lap (100%).	IA: 0% (0/9)	IIA: 12% (6/50)	IIIA: 18% (7/40)	Randomized: cobalt EFRT alone (16%, 11/67) vs CMT: LFRT followed by 3-6× MOPP (16%, 7/44)	E-lesions were associated with significantly more relapses, shorter remission duration, and worse OS in EFRT-only group but not in CMT group. Strong association between lung E-lesions, moderate to large mediastinal masses, and subsequent marginal recurrences.
										na	IIB: 42% (5/12)	na		
	1982	Wiernik and Slawson	23‡	1966-1981	177 (62 unique)	nd	Ann Arbor	Majority pulmonary involvement by direct extension from MMT	Chest tomog; lap (100%).	I-III: 33/177 (19%)			Randomized to EFRT alone (19%, 20/106) vs CMT: RT and 6× MOPP (18%, 13/71)	
3	1982	Hoppe et al	25‡	1968-1978	230	nd	Ann Arbor	Lung (28), pleura (2), bone (6), pericardium (13), soft tissue (5), and myocardium (1)	CXR (90%); LAG, lap (100%).	I/II: 17% (40/230)		na	Randomized per H1, H2, H4, R1, K1, S1, S2, and S3: EFRT alone (8%, 9 of 109) vs CMT (26%, 8/121): IFRT (I-IIA), STNI (I-IIA, IIAE), or TLI (I-IIB, IIBE) then MOP(P) or PAVe	E-lesions were not a significant factor for OS or FFR within treatment groups.
	1986	Crnkovich et al	26†	1968-1982	126	26	Ann Arbor	Lung (31), pericardium (14), pleura (11), bone (5), and other (6)	CXR, BMBx, LAG; most chest tomog/CT, lap (94%)	na	IIB: 33% (41/126)	na	TLI (18%, 13/73,); 18 pts CMT (53%, 28/53) most MOPP or PAVe	E-lesions were not a significant factor for 10-year OS and FFR between treatment groups.
4	1984	Zagars and Rubin	56	1969-1981	91	25	Ann Arbor	Lung, pleura, pericardium, and thoracic wall	CXR, w/wo chest tomog/CT, LAG, w/wo lap with splenectomy	IA: nd	IIA:12% (6/51)	na	All RT (TNI or STNI), 8% CMT	E-lesions associated with significantly more relapses in stage IIA treated with RT alone. In 2 cases, mediastinal masses may have driven poor prognosis. In a small portion with CMT, E-lesions did not show negative prognostic implication.
5	1985	Zittoun et al	34	1976-1981	335	(15-74)	Ann Arbor	Mediastinal involvement	CXR, chest tomog, LAG, BMBx	I, II, and IIIA: 6% (20/335)			All CMT: 3×/6× MOPP and randomized to EFRT (4%, 7/166) vs IFRT (8%, 13/169)	Patients with stage IIE disease had significantly worse 5-year DFS than defined low-risk groups.

abd, abdomen; ABVD, adriamycin/bleomycin/vinblastine/dacarbazine; BMA, bone marrow aspirate; BMBx, bone marrow biopsy; Bx, biopsy; C/A/P, chest/abdomen/pelvis; CMT, combined modality therapy; COPP, cyclophosphamide, oncovin, prednison, procabazin; COPDAC, cyclophosphamide, oncovin, prednison, dacarbazin; CR, complete remission; CS, clinical stage; CT, computed tomography; CVRT, consolidation-volume radiotherapy; CXR, chest X-ray; DFS, disease-free survival; eBEACOPP, escalated dose etoposide/cyclophosphamide/doxorubicin and regular doses bleomycin/vincristine/procarbazine/prednisone; EBx, E-lesion biopsy; EFRT, extended field radiotherapy; EFS, event-free survival; FDG, fluorodeoxyglucose, FFP, failure free progression; FFR, freedom from first relapse; FFS, freedom from progression; FFTF, freedom from treatment failure; HD, Hodgkin disease; IFRT, involved field radiotherapy; ISRT, involved site radiotherapy; IPS, international prognostic score; IQR, interquartile range; IVP, intravenous pyelogram; LAG, bipedal lymphangiography; lap, staging laparotomy; LFRT, limited field radiotherapy; LMA, large mediastinal adenopathy; LMT, large mediastinal mass; LN, lymph nodes; L/S, liver/spleen scintiscan; LSF, lumbo-splenic field radiotherapy; MMT, massive mediastinal tumor; MOPP, mustargen/oncovin/procarbazine/prednisone; MPA, mantle and para-aortic splenic pedicle radiotherapy; MRT, mantle radiation therapy; MSI, massive spleen involvement; n, number of cases; na, not applicable; nd, not defined; nia, not included in analysis; NM BS, nuclear medicine bone scan; OEPA, oncovin, etoposide, prednison, anthracyclin (doxorubicin); OPPA, oncovin, procarbazin, prednison, anthracyclin (doxorubicin); PAVe, procarbazine/l-phenylalamine mustard/vinblastine; PFS, progression-free survival; PS, pathologic stage; Ref, reference; RT, radiotherapy; SS, skeletal scan; STNI, subtotal nodal irradiation; TG, treatment group; th, thorax; TLI, total lymphoid irradiation; TNI, total nodal irradiation; tomog, tomography; U/S, ultrasound; x, times; XR, X-ray; and w/wo, with or without.

*Patients with stage IV HL were excluded in this number.

†Because there were overlapping study populations, these data were used for stage-specific incidence calculation.

‡Because there were overlapping study populations, these data were used for overall incidence calculation.

§This study used elevated risk–based criteria for inclusion.

Table 3 (continued)

Study	Year	Author	Reference	Study period	n*	Median age, y (range)	Staging criteria	E-Lesion location (n)	Staging tools	Incidence of E-lesions by stage			Treatment (E/total, % with E-lesion)	Impact of E-lesions on prognosis, notable covariates
										I	II	III		
6	1985	Leslie et al	35	1969-1980	307	(3 to > 40)	Ann Arbor	Lung (13), pericard (5), chest wall (3), and other (4)	CXR w/wo chest tomog/CT, LAG, lap with splenectomy (100%)	IA-IIB supradiaphragmatic: 8% (25/307)		na	IA, IIA: RT alone; IB & IIB: RT alone or CMT with MOPP; RT mostly MPA	When analyzed by mediastinal size, E-lesions did not influence FFR or OS. Among patients with E-stage disease, 11 of 25 had B-symptoms and 13 of 25 had bulk disease.
7	1989	Loeffler et al	28†,§	1983-1988	89	28 (15-56)	Ann Arbor	Mostly massive lung involvement	CXR, abd CT & U/S, BMBx, SS; lap or liver bx/BMBx/LAG; optional: chest CT, L/S, skeletal XR	IA: 0% (0/1)	IIA: 28% (8 of 29); IIB: 24% (5/21)	IIIA: 8% (3/38)	Per HD1: (I-III with LMT, E-stage, and/or MSI): All CMT with 2× ABVD/COPP and EFRT or TNI; bulk RT boost; stage IIIA TNI	E-lesions had no prognostic significance for CR rate, FFTF, OS, or FFP. Six of the patients with stage IIAE disease and 5 of the patients with stage IIBE disease also had MLT.
	1997	Loeffler et al	27‡,§	HD1: 1984-1988	HD1 147	(15-60)	Ann Arbor	nd	CXR, chest CT, abd CT and U of S, BMBx, liver biopsy, NM BS; optional studies: L/S, LAG, skeletal XR (lap recommended in HD1, but not HD5)	HD1, I-IIIA + risk factors: 41% (31/147)			Per HD1 & HD5: (I-III with LMT, E-stage, and/or MSI): all CMT with 2× ABVD/COPP and EFRT or TNI; bulk RT boost	Despite E-lesions not routinely irradiated (lung pleura), there were 100% local CR and no relapses after chemotherapy (median follow-up, 6.5 y).
				HD5: 1988–1993	HD5 111	31 (16-62)				HD5, I-IIIA + risk factors: 27% (30/111)				
8	1989	Leopold et al	36§	1969-1984	92	(9-50)	Ann Arbor	nd	CXR, abd CT or LAG, BMBx, lap and splenectomy (74%, TG 1 and 2)	CS IA-IIB with LMA –> PS IA-IIIB: 29% (27/92)			TG 1: RT only with MPA, TNI, or whole-lung RT (17%, 6/38); TG 2&3: CMT with MOPP and IFRT, MRT, MPA, or TNI (39%, 21/54)	E-lesions had no significant effect on 12-year relapse rate or survival within treatment groups.
9	1992	Oberlin et al	32	1982-1988	217 (IV, 21)	10 (2-18)	Ann Arbor	Pleura (4), pericardium and pleura (1), thoracic wall (2), and lung (3).	CXR w/wo chest CT, LAG, BMBx	I-III: 5% (10/217)			TG1: ABVD only, TG2-4: CMT with ABVD w/wo MOPP, IF-RT w/wo LSF	Four patients with E-lesions (40%) had local relapses, (statistical significance, nd). Two of these had bulky disease.
10	1999	Shah et al	37	1970-1995	106	14 (3-22)	Ann Arbor	nd	CXR, CT C (61%) or CT A (78%) or CT P (73%), L/S (60%), LAG (50%), NM BS (34%), NI (84%), lap (60%), w/wo BMBx	Supradiaphagmatic I/II: 3% (3/106)		na	RT, IFRT, mantle only, TNI, STNI	E-lesions had no significant influence on relapse rate, OS, or EFS.
11	2000	Franklin et al	18§	1988-1994	712	(15-75)	Ann Arbor	nd	nd	I-IIIA: 12% (85 of 712)			Per HD5: CMT with COPP/ABVD or COPP/ABV/IMEP, followed by EFRT, bulk RT boost	Patients with E-lesions, especially IIBE and IIIE, had a poor prognosis at 5 years. E-lesions were a significant poor prognostic factor beyond IPS.
										na	IIB-IIIA: 5% (35/712)			

abd, abdomen; ABVD, adriamycin/bleomycin/vinblastine/dacarbazine; BMA, bone marrow aspirate; BMBx, bone marrow biopsy; Bx, biopsy; C/A/P, chest/abdomen/pelvis; CMT, combined modality therapy; COPP, cyclophosphamide, oncovin, prednison, procabazin; COPDAC, cyclophosphamide, oncovin, prednison, dacarbazin; CR, complete remission; CS, clinical stage; CT, computed tomography; CVRT, consolidation-volume radiotherapy; CXR, chest X-ray; DFS, disease-free survival; eBEACOPP, escalated dose etoposide/cyclophosphamide/doxorubicin and regular doses bleomycin/vincristine/procarbazine/prednisone; EBx, E-lesion biopsy; EFRT, extended field radiotherapy; EFS, event-free survival; FDG, fluorodeoxyglucose, FFP, failure free progression; FFR, freedom from first relapse; FFS, freedom from progression; FFTF, freedom from treatment failure; HD, Hodgkin disease; IFRT, involved field radiotherapy; ISRT, involved site radiotherapy; IPS, international prognostic score; IQR, interquartile range; IVP, intravenous pyelogram; LAG, bipedal lymphangiography; lap, staging laparotomy; LFRT, limited field radiotherapy; LMA, large mediastinal adenopathy; LMT, large mediastinal mass; LN, lymph nodes; L/S, liver/spleen scintiscan; LSF, lumbo-splenic field radiotherapy; MMT, massive mediastinal tumor; MOPP, mustargen/oncovin/procarbazine/prednisone; MPA, mantle and para-aortic splenic pedicle radiotherapy; MRT, mantle radiation therapy; MSI, massive spleen involvement; n, number of cases; na, not applicable; nd, not defined; nia, not included in analysis; NM BS, nuclear medicine bone scan; OEPA, oncovin, etoposide, prednison, anthracyclin (doxorubicin); OPPA, oncovin, procarbazin, prednison, anthracyclin (doxorubicin); PAVe, procarbazine/l-phenylalamine mustard/vinblastine; PFS, progression-free survival; PS, pathologic stage; Ref, reference; RT, radiotherapy; SS, skeletal scan; STNI, subtotal nodal irradiation; TG, treatment group; th, thorax; TLI, total lymphoid irradiation; TNI, total nodal irradiation; tomog, tomography; U/S, ultrasound; x, times; XR, X-ray; and w/wo, with or without.

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Table 3 (continued)

Study	Year	Author	Reference	Study period	n*	Median age, y (range)	Staging criteria	E-Lesion location (n)	Staging tools	Incidence of E-lesions by stage			Treatment (E/total, % with E-lesion)	Impact of E-lesions on prognosis, notable covariates
										I	II	III		
	2002	Sieber et al	29‡,§	1988-1993	973	31 (16-74)	Ann Arbor	nd	CXR, CT C/A/P, BMBx, liver bx	I, II, and IIIA: 12% (113/973)				7-year FFTF and CR rate significantly worse in both treatment arms.
12	2001	Ruhl et al	33	1995-2000	730 (IV, 100)	14 (maximum 18)	Cotswolds revision of Ann Arbor	Pleura, pericardium, and anterior thoracic wall	CXR, chest CT, abd CT/MRI; US th/ abd/ LN; w/wo neck CT/MRI, NM BS, BMBx, lap/liver bx	0% (0/58)	IIA: 27% (100/365)	IIIA: 33% (25/75)	Per GPOH-HD 95: all 2× OEPA/OPPA, w/wo 2× or 4× COPP; response-adapted IFRT	E-lesions were a significant risk factor for both progressive disease and relapse.
										na	IIB: 53% (66/125)	IIIB: 27%(25/91)		
13	2002	Dieckmann et al	15	1990-1995	518 (IV, 60), precentral review	12 (2-17)	Ann Arbor	Pericardium, lung, chest wall, and pleura.	CXR, CT C/A/P, U/S (neck, axilla, abd, pelvis), w/wo lap, w/wo BMBx	IA: 1% (1/98); IB: 0% (0/7)	IIA: 9% (20/218); IIB: 18% (14/78)	IIIA: 12% (7/59); IIIB: 15% (9 of 58)	Per GPOH-HD-90: TG1 (I/IIA) 2× OPPA (females) or OEPA (males); TG2 (IIB/IIIA/IE/IIEA); 4× OPPA (females) or OEPA (males); TG3 (IIIB/IV/IIEB/IIIE) 6× OPPA (females) or OEPA (males); all groups received local RT to initially involved areas (25 Gy TG 1&2; 20 Gy TG3; w/wo 5-10 Gy boost)	nia
					494 (IV, 84), postcentral review					IA: 0% (0/89); IB: 0% (0/5)	IIA: 15% (33/214); IIB: 37% (29/78)	IIIA: 24% (13/55); IIIB: 21% (11/53)		
14	2003	Glimelius et al	38	1985-1994	99	33 (17-59)	Ann Arbor	nd	CXR, CT C/A/P, abd US, BMBx	na	IIB: 11% (11/99)	na	CT 6-8× MOPP/ABVD, RT	Not significant in 10-year DFS and HL-specific survival
15	2003	Hodgson et al	39	1981-1996	324	29 (15-78)	Ann Arbor	Lung or chest wall.	Chest CT	I-II: 12% of (40/324) lung invasion		na	All CMT	5-year OS: no significant effect
										I-II: 7% (22/324) of chest-wall invasion				Chest wall significantly worse; 5-year CSS and DFS: lung extension no significant effect
16	2004	Hudson et al	40§	1993-2000	115 (IV, 44)	15 (2-19)	Ann Arbor	nd	CXR, CT with contrast neck/ C/A/P (or MRI for A/P)	I-II with risk factors or III: 10% (11/115)			na	E-lesions were not distinguished from stage IV disease with analysis regarding extranodal involvement.

abd, abdomen; ABVD, adriamycin/bleomycin/vinblastine/dacarbazine; BMA, bone marrow aspirate; BMBx, bone marrow biopsy; Bx, biopsy; C/A/P, chest/abdomen/pelvis; CMT, combined modality therapy; COPP, cyclophosphamide, oncovin, prednison, procabazin; COPDAC, cyclophosphamide, oncovin, prednison, dacarbazin; CR, complete remission; CS, clinical stage; CT, computed tomography; CVRT, consolidation-volume radiotherapy; CXR, chest X-ray; DFS, disease-free survival; eBEACOPP, escalated dose etoposide/cyclophosphamide/doxorubicin and regular doses bleomycin/vincristine/procarbazine/prednisone; EBx, E-lesion biopsy; EFRT, extended field radiotherapy; EFS, event-free survival; FDG, fluorodeoxyglucose, FFP, failure free progression; FFR, freedom from first relapse; FFS, freedom from progression; FFTF, freedom from treatment failure; HD, Hodgkin disease; IFRT, involved field radiotherapy; ISRT, involved site radiotherapy; IPS, international prognostic score; IQR, interquartile range; IVP, intravenous pyelogram; LAG, bipedal lymphangiography; lap, staging laparotomy; LFRT, limited field radiotherapy; LMA, large mediastinal adenopathy; LMT, large mediastinal mass; LN, lymph nodes; L/S, liver/spleen scintiscan; LSF, lumbo-splenic field radiotherapy; MMT, massive mediastinal tumor; MOPP, mustargen/oncovin/procarbazine/prednisone; MPA, mantle and para-aortic splenic pedicle radiotherapy; MRT, mantle radiation therapy; MSI, massive spleen involvement; n, number of cases; na, not applicable; nd, not defined; nia, not included in analysis; NM BS, nuclear medicine bone scan; OEPA, oncovin, etoposide, prednison, anthracyclin (doxorubicin); OPPA, oncovin, procarbazin, prednison, anthracyclin (doxorubicin); PAVe, procarbazine/l-phenylalamine mustard/vinblastine; PFS, progression-free survival; PS, pathologic stage; Ref, reference; RT, radiotherapy; SS, skeletal scan; STNI, subtotal nodal irradiation; TG, treatment group; th, thorax; TLI, total lymphoid irradiation; TNI, total nodal irradiation; tomog, tomography; U/S, ultrasound; x, times; XR, X-ray; and w/wo, with or without.

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Study	Year	Author	Reference	Study period	n*	Median age, y (range)	Staging criteria	E-Lesion location (n)	Staging tools	Incidence of E-lesions by stage			Treatment (E/total, % with E-lesion)	Impact of E-lesions on prognosis, notable covariates
										I	II	III		
17	2004	Vassilakopoulos et al	41	1980-2001	367	30 (14-82)	Ann Arbor	nd	CXR, CT C/A/P, LAG, BMBx	IA & IIA: 5% (20/367)		na	MOPP (8%, 5/65) or E(A)BVD (5%, 15/302) then RT (89% IFRT)	In A(E)BVD subgroup (but not all patients), E disease was an independent predictor of poorer 10-year FFS. E disease status did not impact 10-year OS.
18	2005	Gisselbrecht et al	42	nd	1156	30 (14-69)	Cotswolds revision of Ann Arbor	nd	nd	I-II: 8% (91/1156)		na	Per H8 (36/518) 3-6× MOPP/ABV, then IFRT or STNI; per H9 (55/638): CMT with 6× EBVP, 4-6× ABVD, or 4× BEACOPP, then IFRT	E-lesions associated with significantly worse OS at 42 months. Authors hypothesize E disease may be surrogate for bulky mediastinal disease
19	2007	Gallamini et al	43	2001-2006	216 (IV, 44)	32 (14-72)	Cotswolds revision of Ann Arbor	nd	CXR, CT C/A/P, LAG, FDG-PET	6% (4 of 67)	10% (7/70)	24% (19/79)	na	E-lesions were not distinguished from stage IV disease with analysis regarding extranodal involvement.
20	2011	Wirth et al	48	1999-2001	148	33 (18-75)	Cotswolds revision of Ann Arbor	nd	CT, BMBx	I-II: 3% (5/148)		na	3-4× ABVD, IFRT	Significant factor for worse OS and FFS at 5 years
21	2012	Gobbi et al	49§	nd	129	34 (20-48)	Cotswolds revision of Ann Arbor	nd	CT with contrast neck/C/A/P	IA, IB, IIA + risk factors: 8% (10/129)	IIB, III, and IV taken together in analysis		4-6× ABVD, IFRT	For early, unfavorable disease, presence of E-lesions was the only statistically important predictor of early treatment failure beyond relative tumor burden.
22	2013	Song et al	50	2006-2011	127	42 (18-78)	Cotswolds revision of Ann Arbor	nd	CT neck/C/A/P, BMBx, FDG-PET/CT	I-II: 24% (30/127)		na	4-6× ABVD and IF-RT or 6 ABVD	E-lesion not a significant factor for PFS nor OS at 45 months.
23	2014	Laskar et al	44§	2000-2008	151	20 (3-70)	Cotswolds revision of Ann Arbor	nd	CT	IA: 0% (0/38)	IIA: 3% (3/96)	na	4-6× ABVD and IFRT	E-lesions were a significant factor for worse 10-year PFS and OS among patients with early unfavorable disease.
										IB: 0% (0/13)	IIB: 0% (0/4)	na		
24	2018	Gaudio et al	46	2006-2017	384 (IV w/ bone involvement, 27/32; 85%).	36 (15-83)	Ann Arbor	E-lesion vs stage IV sites nd	CXR, CT-CAP, FDG-PET/CT–total body, unilateral BMBx	I/II w/ bone involvement: 3% (1/32)		III w/ bone involvement: 12% (4/32)	ABVD w/wo RT	E-lesions were not distinguished from stage IV disease with analysis regarding extralymphatic involvement.
25	2018	Gaudio et al	45	2006-2016	Stage I-II: 235 (III/IV, 106)	36 (15-83)	Ann Arbor	E-lesion vs stage IV sites nd	CXR, CT-CAP, FDG-PET/CT–total body, unilateral BMBx	I/II: 3% (7/235)		III/VI	ABVD w/wo IFRT	E-lesions were not distinguished from stage IV disease with analysis regarding extralymphatic involvement.

abd, abdomen; ABVD, adriamycin/bleomycin/vinblastine/dacarbazine; BMA, bone marrow aspirate; BMBx, bone marrow biopsy; Bx, biopsy; C/A/P, chest/abdomen/pelvis; CMT, combined modality therapy; COPP, cyclophosphamide, oncovin, prednison, procabazin; COPDAC, cyclophosphamide, oncovin, prednison, dacarbazin; CR, complete remission; CS, clinical stage; CT, computed tomography; CVRT, consolidation-volume radiotherapy; CXR, chest X-ray; DFS, disease-free survival; eBEACOPP, escalated dose etoposide/cyclophosphamide/doxorubicin and regular doses bleomycin/vincristine/procarbazine/prednisone; EBx, E-lesion biopsy; EFRT, extended field radiotherapy; EFS, event-free survival; FDG, fluorodeoxyglucose, FFP, failure free progression; FFR, freedom from first relapse; FFS, freedom from progression; FFTF, freedom from treatment failure; HD, Hodgkin disease; IFRT, involved field radiotherapy; ISRT, involved site radiotherapy; IPS, international prognostic score; IQR, interquartile range; IVP, intravenous pyelogram; LAG, bipedal lymphangiography; lap, staging laparotomy; LFRT, limited field radiotherapy; LMA, large mediastinal adenopathy; LMT, large mediastinal mass; LN, lymph nodes; L/S, liver/spleen scintiscan; LSF, lumbo-splenic field radiotherapy; MMT, massive mediastinal tumor; MOPP, mustargen/oncovin/procarbazine/prednisone; MPA, mantle and para-aortic splenic pedicle radiotherapy; MRT, mantle radiation therapy; MSI, massive spleen involvement; n, number of cases; na, not applicable; nd, not defined; nia, not included in analysis; NM BS, nuclear medicine bone scan; OEPA, oncovin, etoposide, prednison, anthracyclin (doxorubicin); OPPA, oncovin, procarbazin, prednison, anthracyclin (doxorubicin); PAVe, procarbazine/l-phenylalamine mustard/vinblastine; PFS, progression-free survival; PS, pathologic stage; Ref, reference; RT, radiotherapy; SS, skeletal scan; STNI, subtotal nodal irradiation; TG, treatment group; th, thorax; TLI, total lymphoid irradiation; TNI, total nodal irradiation; tomog, tomography; U/S, ultrasound; x, times; XR, X-ray; and w/wo, with or without.

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Table 3 (continued)

Study	Year	Author	Reference	Study period	n*	Median age, y (range)	Staging criteria	E-Lesion location (n)	Staging tools	Incidence of E-lesions by stage			Treatment (E/total, % with E-lesion)	Impact of E-lesions on prognosis, notable covariates
										I	II	III		
26	2019	Casasnovas et al	47§|	2011-2014	823	30 (16-30)	Ann Arbor	nd	CXR; PET/CT head/neck/C/A/P; BMA	na	IIB: 11% (10/87)	na	Per AHL2011: 6× eBEACOPP vs 2× eBEACOPP then PET-driven BEACOPP and/or ABVD	nia
27	2020	Myint et al	51	2005-2014	293	40 (18-85)	Ann Arbor	nd	nd	IA/IIA: 1% (2/293)		na	Chemotherapy alone vs CMT	E-lesion inclusion in multivariate survival modeling is not explicitly stated.
					130	35 (18-88)				IB/IIB: 3% (4/130)				
28	2021	Picardi et al	52	2017-2019	60	40 (18-70)	Ann Arbor classification with Lugano modification	nd	Same-day FDG- PET/CT, followed by FDG-PET/unenhanced MRI C/A/P; BMBx, U/S	0% (0/8)	1% (2/22)	na	2-6× ABVD and IFRT (I/II) or residual mass RT	nia
29	2021	Kumar et al	53§	2013-2019	117	32 (18-59)	Ann Arbor	Pericardial, chest wall, and sternum	PET	na	TG 1&2, II: 25% (15/59)	na	Brentiximab-vedotin + AVD ×4 cycles w/wo RT (TG 1&2 ISRT, TG3 CVRT)	No clear impact of E-lesions; 1 of 7 patients with primary refractory/relapsed disease had stage IIBXE disease. All patients had risk factors, with TG 2-4 (86% overall) having bulky (>7 cm) disease.
										TG 3&4, I-II : 16% (9/56)				
30	2022	Mauz-Korholz et al	30	2007-2013	TG2&3: 793 (IV, 494)	14 (IQR, 12-16)	Cotswolds revision of Ann Arbor	nd	CT with contrast neck/C/A/P (or MRI neck/A/P), FDG-PET	na	IIA: 97% (93/96)	IIIA: 16% (30/187)	Per EuroNet-PHL-C1: TG1: OEPA ×2; TG2: OEPA ×2 –> COPP or COPDAC ×2; TG3: OEPA ×2 –> COPP or COPDAC ×4; early response assessment-based w/wo IFRT w/wo residual RT boost	nia
										na	IIB: 37% (114/308)	IIIB: 27% (54/202)		
	2023	Mauz-Korholz et al	31		TG1: 713	14 (IQR, 12-16)				IA: 0% (0/40)	IIA:<1% (1/666)	IIIA: 0% (0/1)		
										IB: 0% (0/5)	IIB: 0% (0/1)	x		
31	2021	Borchmann et al	54§	2012-2017	1096	31 (18-60)	Ann Arbor	nd	PET-CT	I-II with risk factor: 8% (89/1096)		na	Per HD17: 2× eBEACOPP + 2× ABVD; IFRT or PET-guided INRT	nia

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during a similar time period. The Hoppe article reported on patients with stage I-II HL. The Crnkovich article appeared to include a longer-term follow-up of a subset (stage IIB) of the same patients. The only stage-specific E-lesion incidence data available was from the Crnkovich article. To avoid double counting patients, only the larger population reported by Hoppe was used for the overall incidence calculation. Both articles were used in the prognosis analysis because they provided unique outcomes analyses.

A third set of overlapping populations studied by Loeffler et al[27,28] reported unique prognostic data from patients treated on the German HD1 study. The only stage-specific data available were from the 1989 article. To avoid double counting of patients, we used the 1997 article (with the larger population) in the overall incidence calculation.

The final set of overlapping populations were patients treated on the German HD5 treatment protocol described by Franklin[18] and Sieber.[29] Both articles were included because they each described discrete prognostic data. To avoid double counting patients, only the larger population reported by Sieber was used for the overall incidence calculation.

Table 3 denotes which of the overlapping studies were used for incidence calculations. Because the presence of E-lesions was used to determine EuroNet PHL-C1 treatment groups, the stage-specific incidence data from the separate articles[30,31] were interpreted as a single study population. All articles included in our final analysis were published between 1977 and 2022.

Participant characteristics

In the 36 articles analyzed, 12 640 patients (aged 2-88 years) with stage I-III HL were included. Five articles included solely pediatric patients (aged 0-18 years),[15,30-33] 19 articles included children and adults,[18,22,27-29,34-47] 7 included only adults,[48-54] and 5 articles[23,25,26,55,56] provided limited information about patient age.

Definition of E-Lesions

We observed that 26 articles used the Ann Arbor criteria for staging classification,[12,15,18,22,23,25-29,32,34-41,45-47,51,53-56] 9 articles used the Cotswolds revision of the Ann Arbor staging classification,[30,33,42-44,48-50] and 1 study used the Lugano criteria.[52] Fourteen studies provided some description of E-lesion location.[12,22,23,25,26,28,32-35,39,45,46,53,56]

Diagnostic tools

A wide variety of imaging modalities were used in these studies because of the evolution of imaging technology over time. Studies used a combination of X-ray imaging, CT (or focal plane tomography), nuclear medicine (liver spleen scan, positron emission tomography [PET], and bone scan), ultrasound, and MRI, in addition to surgical sampling (biopsies, laparotomies, and splenectomies) for staging. Several studies in our analysis concluded that CT scanning was more sensitive than X-ray imaging for the detection of E-lesions of the lung parenchyma, pleura, pericardium, and chest wall.[57-61] Gaudio et al noted more extranodal localizations were found with the use of PET/CT than with contrast-enhanced CT for staging.[45] One pediatric article reported their findings with full-body MRI with diffusion-weighted imaging for staging in 50 pediatric patients with HL (aged 5-19 years) enrolled on Euronet PHL-C1 or PHL-LP1 trials and concluded that the technology was not acceptably equivalent to PET-CT for staging purposes (Ann Arbor staging concordant in 78%, 39/50),[62] including at extranodal sites (28% discordance rate; 95% confidence interval exact, 17.8-40.3).[62]

Incidence of E-lesions by stage

In the 36 articles analyzed, 1330 of the 11 602 unique patients (12.4%) had an E-lesion (results summarized in Table 4). Sixteen articles[15,22,26,28,30,31,33,38,43,44,46,47,52,53,55,56] encompassing 3888 patients provided stage-specific E-lesion incidence data. E-lesions were rarely present in stage I disease, affecting 1.1% (4/365) of patients (range, 0%-6%). Available data did not show a difference in incidence between IA and IB subgroups. E-lesions were similarly prevalent in stage II and III disease, affecting 21.2% (560/2646) of patients (range, 0%-53%) and 21.9% (192/877) of patients (range, 4%-33%), respectively. Overall, there were notably more E-lesions in patients with stage IIB disease (32.4% [284/877]; range, 0%-53%) than in those with stage IIA disease (15.6% [252/1618]; range, 3%-28%). A similar relationship was seen with more E-lesions in patients with stage IIIB disease (26.0% [90/346]; range, 21%-27%) than in those with stage IIIA disease (18.8% [79/420]; range, 4%-33%).

Nine studies[18,27,36,40,44,47,49,53,54] used risk-based inclusion criteria, including a combination of stage, bulk disease (mediastinal or other sites), extranodal disease, B-symptoms, massive spleen involvement, or GHSG unfavorable early-stage disease. When these studies were excluded, the overall and stage-specific incidence of E-lesions were relatively unchanged (stage I-III: 12.5% [982/7848]; stage I: 1.3%, stage II: 21.7%, stage III: 22.5%).

Table 4. Summary of incidence of E-lesions by stage

Stage	n (E/total)	Percentage	Range (%)
I	4/365	1.1	0-6
IA	*0/258*	*0*	*0-0*
IB	*0/32*	*0*	*0-0*
II	**560/2646**	**21.2**	**0-53**
IIA	*252/1618*	*15.6*	*3-28*
IIB	*284/877*	*32.4*	*0-53*
III	**192/877**	**21.9**	**4-33**
IIIA	*79/420*	*18.8*	*4-33*
IIIB	*90/346*	*26.0*	*21-27*
When high risk–based studies were excluded:			
Stage	**n (E/total)**	**Percentage**	**Range (%)**
I	**4/313**	**1.3**	**0-6**
IA	*0/219*	*0*	*0-0*
IB	*0/19*	*0*	*0-0*
II	**529/2437**	**21.7**	**4-53**
IIA	*241/1493*	*16.1*	*4-27*
IIB	*279/852*	*32.7*	*11-53*
III	**189/839**	**22.5**	**4-33**
IIIA	*76/382*	*19.9*	*4-33*
IIIB	*90/346*	*26.0*	*21-27*

Italicized results are subclassification-specific data. The bolded results also include data that did not specify the absence or presence of B symptoms. Studies using elevated risk–based criteria for inclusion are denoted with "§" in Table 3 or "*" in Table 5.

Treatment and prognosis

Twenty-two articles, encompassing 5836 patients, examined the prognostic implication of E-lesions (Table 5). Eight articles[18,29,33,34,42,44,48,49] (3622 patients) found the presence of E-lesions to be predictive of poorer outcomes, including relapse and survival metrics. All patients in this subset received CMT, except patients in 2 studies[33,42] in which response-adapted radiotherapy was also used. The interim report of the prospective, nonrandomized German Society of Pediatric Oncology and Hematology Hodgkin Lymphoma Trial 95 examining response-adapted involved field radiotherapy in pediatric early-stage HL found E-lesions to be an independent risk factor for both progressive disease ($P < .002$) and relapse ($P < .002$) at a median follow-up of 38 months.[33] Two articles[18,29] similarly commented on the association of E-lesions and poor relapse outcomes in the HD5 trial, which evaluated different CMT regimens in patients with stage I-II HL with GHSG risk factors, or with stage III HL. E-lesion also trended toward providing additional prognostic value beyond the International Prognostic Score for disease-free survival, reaching statistical significance for stage IIB-IIIA HL; the authors speculate this may be related to misclassification between the sometimes subtle distinction between E-lesion and stage IV disease.[18] Another study comparing cooperative group risk criteria used pooled outcomes from H8 and H9 randomized trials found E-lesions to be associated with significantly worse overall survival at 42 months in patients with stage I-II disease largely treated with CMT (multivariate, stage–adjusted prognostic index, relative risk [RR], 1.2; $P = .008$), but the authors hypothesized that bulky mediastinal disease may be the driver of the poor outcomes in these patients.[42]

Nine articles,[25-28,35-38,50] encompassing 1345 patients, reported that the presence of E-lesions did not influence relapse or survival outcomes. Patients in this subgroup received either radiation monotherapy or CMT. Leslie et al[35] noted the frequent cooccurrence of B-symptoms (11/25) and bulk disease (13/25) in those with E-lesions; when patients were analyzed by mediastinal size, E-lesions did not appear to influence freedom from relapse or 10-year survival. Leopold et al[36] retrospectively evaluated 92 patients with stage IA-IIB disease with large mediastinal adenopathy that was treated with radiation monotherapy or CMT; the substantial subset of patients with E-lesions (29%) did not have significantly different 12-year relapse rate or overall survival.

Five articles,[22,23,39,41,56] encompassing 869 patients, described nuanced prognostic relationships between study groups. Hodgson et al[39] noted that in patients with stage I-II HL treated with CMT, the site of extranodal extension determined the impact on disease outcomes; patients with chest-wall E-lesions but not lung E-lesions had poorer cause-specific and overall survival compared with those with only nodal disease. Three articles[22,23,56] reported that the unfavorable association between E-lesions and remission duration, disease-free survival, and OS were negated when CMT was administered instead of radiation alone; authors note that many of the patients with E-lesions also had large mediastinal masses that may have been the driver of their poor outcomes. Vassilakopoulos et al[41] found that the presence of E-lesions was an independent predictor of poorer 10-year failure-free survival in patients with stage IA-IIA HL treated with adriamycin(epirubicin)/bleomycin/vinblastine/dacarbazine and radiation, but the statistical significance did not hold once patients treated with mustine, oncovin, prednison, procarbazin (MOPP) were also included; E-lesions were not associated with 10-year overall survival in either group.

Pediatric studies

Five articles included only pediatric patients, with a maximum patient age of 18 years.[15,30-33] All studies included patients with stage I-III HL. The incidence of E-lesions was 20.5% [604/2947]; range, 5% to 30%. Two of these articles[15,32] used the Ann Arbor classification for staging, whereas 3 articles[31,33] used the Cotswold modification; all 5 provided a specific definition of E-lesions in their methods or protocols. Four articles[15,31,33] used CT as a diagnostic tool for all patients, and 1 study[32] used CT for some patients. One study[33] included information about the impact of E-lesions on prognosis, which concluded that E-lesions were a negative prognostic risk factor for progressive disease and relapse after a median follow-up period of 38 months.

Discussion

Our review of the literature has shown that the term "extranodal involvement" is frequently ambiguously used to refer to either locally contiguous disease or disseminated involvement. For example, Dieckmann et al[15] clarifies that "extralymphatic involvement" included multiple scenarios: contiguous spread, noncontiguous spread, involvement of multiple sites, and diffuse involvement. Care should be taken in future manuscripts to carefully define terminology used to allow for interpretation of the significance of extension to an extranodal site. Although the appropriate use of "extranodal involvement" or "extralymphatic involvement" can be inferred when working within the boundaries of stage I-III disease, the inclusion of stage IV disease creates ambiguity. The term "E-lesion" or "extranodal extension" should be used within manuscripts (including tables) when referring to localized (contiguous) disease.

E-lesions were similarly prevalent in stage II and III, and more often seen with B symptoms; E-lesions were rarely seen in stage I disease. Although E-lesions can occur in stage IV disease, nonspecific language prevented further investigation. The inconsistent prognostic implications of E-lesions were not clearly explained by treatment era, therapies received, or risk-based inclusion criteria, although a combination of these factors could obscure their effects. The largest studies (and overwhelming cumulative population), with presumably the greatest power to detect an effect, showed that E-lesions were a negative prognostic factor.[18,29,33,42] The apparent trend of greater incidence of E-lesions in patients with B symptoms and the previously described associations with E-lesions and mediastinal and/or bulk disease[22,23,35,42,56] further support the need for careful description and control of other known risk factors (eg, peripheral vs mediastinal bulk) to elucidate the prognostic influence of E-lesions in the current treatment era.

It is important to note the limitations of including studies across a wide range of diagnostic and therapeutic technological eras. As imaging technologies evolved, the sensitivity of detecting small areas of extranodal extension increased. CT scans were more sensitive than X-ray imaging for detecting E-lesions.[57-61] The limited imaging obtained in many of the early studies would be considered insufficient to adequately stage patients today. Current CT, MRI, and PET modalities are all able to detect E-lesions, and a combination should be used to image the neck, chest, abdomen,

Table 5. Studies grouped by E-lesion prognostic influence

No	Year	Author	Reference	Impact of E-lesions on prognosis and noted covariates	Treatment	OS	DFS/PFS/FFTF	Relapse rate	CR/duration/other outcomes
A. Studies concluding E-lesions are a poor prognostic factor under nuanced circumstances									
2	1977	Levi et al	22	E-lesions were associated with significantly more relapses, shorter remission duration, and worse OS in EFRT-only group but not CMT group. Strong association between lung E-lesions, moderate to large mediastinal masses, and subsequent marginal recurrences.	RT	4-year OS worse with E-lesion RT-only group: nodal ~87% vs E-lesion ~56% ($P \leq .01$)	Significantly shorter remission duration for the patients with "E"-stage disease when extended field irradiation was the initial therapy ($P < .002$)	Relapse after 5 years: 29% nodal disease (14/48) vs 82% with E-lesions (9/11)	3-year CR duration: nodal ~71% vs E-lesion ~18%
					CMT	5-year OS not significantly different with CMT: nodal ~100% vs E-lesion ~97% ($P > .10$)	No significant difference between the 2 patient groups when initial therapy was CMT ($P > .35$)	Relapse after 5 years: nodal disease (6%, 2/36) vs E-lesions (14%, 1/7)	5-year CR duration: nodal ~95% vs E-lesion ~86%
	1982	Wiernik and Slawson	23		RT	12-year OS: nodal ~90% vs E-lesion ~60% ($P < .03$)	12-year DFS of original 115 pts: Nodal 78% vs E-lesion 28% ($P = .002$)	nd	12-year CR duration: Nodal ~83% vs E-lesion ~38% ($p = 0.001$)
					CMT	12-year OS: nodal ~98% vs E-lesion ~93% ($P > .4$)	12-year DFS of original 115 pts: nodal 84% vs E-lesion 94% ($P = .002$)	nd	12-year CR duration: nodal ~97% vs E-lesion ~90% ($P > .3$)
4	1984	Zagars and Rubin	56	E-lesions associated with significantly more relapses in stage IIA treated with RT alone. In 2 cases, mediastinal masses may have driven poor prognosis. In small portion with CMT, E-lesions did not show negative prognostic implication.	RT vs CMT	nd	nd	Significantly more relapses, $P < .05$	nd
15	2003	Hodgson et al	39	5-year OS: no significant effect	CMT	nd	5-year DFS: no E-lesion (84%) vs chest wall (59%) ($P = .016$)	nd	5-year cause-specific survival: No E (94%) vs chest wall (86%) ($P = .009$)
				Chest wall significantly worse; 5-year CSS and DFS: lung extension no significant effect	CMT	5-year OS: 90% no E-lesion, 82% chest-wall invasion ($P = .095$), 88% lung invasion ($P = .386$)	5-year DFS: no E (84%) vs lung invasion (80%) ($P = .47$)	nd	5-year cause-specific survival: No E (94%) vs lung invasion 92% ($P = .25$)
17	2004	Vassilakopoulos et al	41	In A(E)BVD subgroup (but not all patients), E disease was an independent predictor of poorer 10-year FFS. E disease status did not impact 10-year OS.	CMT	nd	10-year FFS: A(E)BVD subgroup, no (87%) vs (73%) ($P = .03$)	nd	FFTF in patients who achieved CR, CR, or VGPR and received low-dose RT, E-lesion prognostic factor $P < .001$ in all treatment groups.
					CMT	10-year OS: all patients, no E (86%) vs E (94%) ($P = .30$); A(E)BVD only, no E (93%) vs E (100%) ($P = .37$)	10-year FFS: all patients, no E (85%) vs E (75%) ($P = .11$)	nd	nd

A(E)BVD, adriamycin(epirubicin)/bleomycin/vinblastine/dacarbazine; chemo, chemotherapy; CI, confidence interval; CMT, combined modality therapy; coef, coefficient; COPP, cyclophosphamide, oncovin, prednison, procarbazin; CR, complete remission; CSS, cause specific survival; DFS, disease-free survival; E, epirubicin; EFRT, extended field radiotherapy; EFS, event-free survival; FFP, failure free progression; FFS, freedom from progression; FFTF, freedom from treatment failure; FFR, freedom from first relapse; HR, high risk; IPS, international prognostic score; MLT, large mediastinal tumor; nd, not defined; pts, patients; PFS, progression-free survival; RR, relative risk; RT, radiotherapy; VGPR, very good partial remission.

*Study used elevated risk–based criteria for inclusion

Table 5 (continued)

No	Year	Author	Reference	Impact of E-lesions on prognosis and noted covariates	Treatment	OS	DFS/PFS/FFTF	Relapse rate	CR/duration/other outcomes
B. Studies concluding E-lesions are not a prognostic factor									
3	1982	Hoppe et al	25	E-lesions were not a significant factor for OS or FFR within treatment groups.	RT	5-year OS: E-lesions, 100% vs all patients, 96%	5-year FFR: E-lesions, 78% vs all patients, 79%	nd	nd
					CMT	5-years OS: E-lesions, 88% vs all patients, 92%	5-year FFR: E-lesions, 90% vs all patients, 87%	nd	nd
	1986	Crnkovich et al	26	E-lesions were not a significant factor for 10-year OS and FFR between treatment groups.	RT	10-year OS: RT arm, 87% vs all patients, 87%	10-year FFR: RT arm, 70% vs all patients, 71%	nd	nd
					CMT	10-year OS: E-lesions, 72% vs all patients, 74%	10-year FFR: CMT arm, 71% vs all patients, 79%	nd	nd
6	1985	Leslie et al	35	When analyzed by mediastinal size, E-lesions did not influence FFR or OS. Among patients with E-stage disease, 11 of 25 had B-symptoms and 13 of 25 had bulk disease.	RT or CMT	10-year OS for large mediastinal adenopathy with E vs without E: 85% vs 81%	10-year FFR for large mediastinal adenopathy with E vs without E: 62% vs 58%	nd	nd
						10-year OS for small mediastinum with E vs without E: 80 vs 84%	10-year FFR for small mediastinum with E vs without E: 85% vs 81%	nd	nd
7	1989	Loeffler et al	28*	E-lesions had no prognostic significance for CR rate, FFTF, OS, or FFP. Six of the patients with stage IIAE disease and 5 of the patients with stage IIBE disease also had MLT.	CMT	3-year OS: no influence of E-lesions	FFTF: all patients vs E, 20% vs 25%, not significant	nd	CR rate: all patients vs E, 83% vs 81%
	1997	Loeffler et al	27*	Despite E-lesions not routinely irradiated (lung and pleura), there were 100% local CR and no relapses after chemotherapy (median follow-up, 6.5 y).	CMT	nd	nd	No relapses after chemotherapy; median follow-up, 6.5 y	100% local CR; median follow-up, 6.5 y
8	1989	Leopold et al	36*	E-lesions had no significant effect on 12-year relapse rate or survival within treatment groups.	RT	12-year OS: no effect in different treatment groups	nd	Relapse rate not significantly different in treatment groups	nd
					CMT	12-year OS: no effect in different treatment groups	nd	Relapse rate not significantly different in treatment groups	nd
10	1999	Shah et al	37	E-lesions had no significant influence on relapse rate, OS, or EFS.	RT	10-year OS: no influence	10-year EFS: no influence	nd	nd

A(E)BVD, adriamycin(epirubicin)/bleomycin/vinblastine/dacarbazine; chemo, chemotherapy; CI, confidence interval; CMT, combined modality therapy; coef, coefficient; COPP, cyclophosphamide, oncovin, prednison, procarbazin; CR, complete remission; CSS, cause specific survival; DFS, disease-free survival; E, epirubicin; EFRT, extended field radiotherapy; EFS, event-free survival; FFP, failure free progression; FFS, freedom from progression; FFTF, freedom from treatment failure; FFR, freedom from first relapse; HR, high risk; IPS, international prognostic score; MLT, large mediastinal tumor; nd, not defined; pts, patients; PFS, progression-free survival; RR, relative risk; RT, radiotherapy; VGPR, very good partial remission.

*Study used elevated risk–based criteria for inclusion

Table 5 (continued)

No	Year	Author	Reference	Impact of E-lesions on prognosis and noted covariates	Treatment	OS	DFS/PFS/FFTF	Relapse rate	CR/duration/other outcomes
14	2003	Glimelius et al	38	Not significant in 10-year DFS and HL-specific survival	CMT	nd	10-year DFS and HL-specific survival not significant	nd	nd
22	2013	Song et al	50	E-lesion not a significant factor for PFS and OS at 45 months.	All chemo, some CMT	Hazard ratio for OS if E-lesion: 2.581; 95% CI, 0.916-7.273; $P = .073$	Hazard ratio for PFS if E-lesion: 1.762; 95% CI, 0.661-4.698; $P = .258$	nd	nd
C. Studies concluding E-lesions are a poor prognostic factor									
5	1985	Zittoun et al	34	Patients with stage IIE disease had significantly worse 5-year DFS than defined low-risk groups.	CMT	nd	5-year DFS: significantly worse for patients with stage IIE (significance not provided).	nd	nd
11	2000	Franklin et al	18*	Patients with E-lesions, especially IIBE and IIIE, had a poor prognosis at 5 years. E-lesions were a significant poor prognostic factor beyond IPS.	CMT	nd	DFS: Cox regression with IPS and additional factors after 5 years: stage IIBE and IIIE significant in addition to IPS ($P = .017$), hazard ratio: 2.62; all E-lesions HR 1.54; $P = .086$	nd	nd
	2002	Sieber et al	29*	7-year FFTF and CR rate significantly worse in both treatment arms.	CMT	nd	7-year FFTF: significantly worse ($P = .015$)	nd	CR duration significantly worse COPP/ABVD arm, 86% vs 94% ($P = .011$) and COPP/ABV/IMEP arm 82% vs 86% ($P \leq .001$)
12	2001	Ruhl et al	33	E-lesions were a significant risk factor for both progressive disease and relapse.	All chemo, some CMT	nd	Risk factor for progressive disease ($P \leq .002$); median follow-up time, 38 mo	Risk factor for relapse ($P < .002$); median follow-up time, 38 mo	nd
18	2005	Gisselbrecht et al	42	E-lesions associated with significantly worse OS at 42 mo. Authors hypothesize E disease may be surrogate for bulky mediastinal disease.	All chemo, most CMT	Multivariate analysis stage–adjusted prognostic index 42-mo OS RR: 1.2 ($P = .008$)	nd	nd	nd
20	2011	Wirth et al	48	Significant factor for worse OS and FFS at 5 y	CMT	5-year OS: no E vs E, 97% (95% CI, 93-100) vs 67% (95% CI, 20-90); $P = .0005$.	5-year PFS: no E vs E: 92% (95% CI, 86-96) vs 50% (95% CI, 11-80); $P = .0002$)	nd	Remained significant factor in multivariate analysis.
21	2012	Gobbi et al	49*	For early, unfavorable disease, presence of E-lesions was the only statistically important predictor of early treatment failure beyond relative tumor burden.	CMT	nd	nd	nd	Early treatment failure predictor in addition to relative tumor burden: E-lesions coef: 0.846; risk, 2.329; $P = .0329$
23	2014	Laskar et al	44*	Significant factor for worse 10-year PFS and OS	CMT	10-year OS: no E (96%) vs E (0%) ($P = .01$)	10-year PFS: E significantly worse ($P = .037$)	nd	nd

A(E)BVD, adriamycin(epirubicin)/bleomycin/vinblastine/dacarbazine; chemo, chemotherapy; CI, confidence interval; CMT, combined modality therapy; coef, coefficient; COPP, cyclophosphamide, oncovin, prednison, procarbazin; CR, complete remission; CSS, cause specific survival; DFS, disease-free survival; E, epirubicin; EFRT, extended field radiotherapy; EFS, event-free survival; FFP, failure free progression; FFS, freedom from progression; FFTF, freedom from treatment failure; FFR, freedom from first relapse; HR, high risk; IPS, international prognostic score; MLT, large mediastinal tumor; nd, not defined; pts, patients; PFS, progression-free survival; RR, relative risk; RT, radiotherapy; VGPR, very good partial remission.

*Study used elevated risk–based criteria for inclusion

and pelvis for staging. Using studies with risk-based HL populations could introduce selection bias, but their absence did not appreciably affect incidence results, and there were no overt trends among prognostic outcomes.

A global consensus has not yet been reached regarding the prognostic influence of E-lesions. Historically, German consortia have been the only groups that use E-lesions in risk stratification,[17] but efforts toward harmonization have led to the recent use of E-lesions in treatment group/level stratification in the EuroNet PHL-C1 and C2 trials, with slight modifications in their E-lesion definitions between trials.[19,20] The presence of bulk disease and/or mediastinal masses are likely covariates that may obscure or inappropriately give prognostic influence of E-lesions. The results of this systematic review demonstrate that E-lesions likely remain predictive, but data from large consortium trials and improved granularity regarding location of E-lesions are needed to confirm this in the modern era of response-adapted therapy. Therefore, the SEARCH for CAYAHL working group proposes an update to the Cotswold-modified Ann Arbor staging criteria to reflect current practices for pediatric HL and to allow for prospective study of harmonized criteria. In conclusion, we propose a definition that an "E-lesion" is a contiguous infiltration of a lymph node mass into extralymphatic structures or organs (eg, lung or bone).[30] Pleural and pericardial involvement should be considered E-lesions, but a pleural or pericardial effusion alone is not considered an "E-lesion." Disease that extends beyond the lymphatic system without adjacent lymphatic involvement is considered stage IV; liver or bone marrow involvement is always considered stage IV disease. Unlike the adult Lugano criteria,[14] E-lesions remain relevant in pediatric patients with stage I, II, and III disease. We recommend that this description of E-lesions should be consistently applied for pediatric patients with HL, with explicit reporting of the presence and location of E-lesions to confirm the prognostic value of E-lesions in the current treatment era.

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Authorship

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A complete list of the SEARCH working group members appears in "Appendix."

ORCID profiles: S.D.V., 0000-0002-2092-2219; K.M., 0009-0002-2580-4171; J.E.F., 0000-0002-4182-9355; A.B., 0000-0002-6482-1823.

Correspondence: Auke Beishuizen, Princess Máxima Center for Pediatric Oncology, Heidelberglaan 25, 3584 CS Utrecht, The Netherlands; email: a.beishuizen-2@prinsesmaximacentrum.nl.

Appendix

The SEARCH working group members are Andishe Attarbaschi, Brad Hoppe, Reena Pabari, Jenny Belsky, Scott Howard, Monica Palese, Auke Beishuizen, Tatum Johnson, Neeta Pandit-Taskar, Nickhill Bhakta, Kara Kelly, Angela Punnett, Steve Cho, Regine Kluge, Jennifer Seelisch, Pedro de Alarcon, Lars Kurch, Dietrich Stoevesandt, Ute (Karin) Dieckmann, Hollie Lai, Paul Thacker, Richard Drachtman, Michael Link, Stephen Voss, Matt Ehrhardt, Lianna Marks, Jamie Zeal, Jamie Flerlage, Christine Mauz-Koerholz, Thomas Georgi, and Kathleen McCarten.

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