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RESEARCH ARTICLE

Differentiation between rebound thymic hyperplasia and thymic relapse after chemotherapy in pediatric Hodgkin lymphoma

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Abbreviations: ^{18}F-FDG, fluorodeoxyglucose; CHL, classical Hodgkin lymphoma; CT, computed tomography; CTX, chemotherapy; EuroNet-PHL, European Network for Pediatric Hodgkin Lymphoma; HL, Hodgkin lymphoma; HU, Hounsfield unit; LR, lymphoma relapse; LRA, late response assessment—staging at the end of CTX; MRI, magnetic resonance imaging; PET, positron emission tomography; RTH, rebound thymic hyperplasia; SUV, standardized uptake value.

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Abstract

Background: Rebound thymic hyperplasia (RTH) is a common phenomenon caused by stress factors such as chemotherapy (CTX) or radiotherapy, with an incidence between 44% and 67.7% in pediatric lymphoma. Misinterpretation of RTH and thymic lymphoma relapse (LR) may lead to unnecessary diagnostic procedures including invasive biopsies or treatment intensification. The aim of this study was to identify parameters that differentiate between RTH and thymic LR in the anterior mediastinum.

Methods: After completion of CTX, we analyzed computed tomographies (CTs) and magnetic resonance images (MRIs) of 291 patients with classical Hodgkin lymphoma (CHL) and adequate imaging available from the European Network for Pediatric Hodgkin lymphoma C1 trial. In all patients with biopsy-proven LR, an additional fluorodeoxyglucose (FDG)-positron emission tomography (PET)-CT was assessed. Structure and morphologic configuration in addition to calcifications and presence of multiple masses in the thymic region and signs of extrathymic LR were evaluated.

Results: After CTX, a significant volume increase of new or growing masses in the thymic space occurred in 133 of 291 patients. Without biopsy, only 98 patients could be identified as RTH or LR. No single finding related to thymic regrowth allowed differentiation between RTH and LR. However, the vast majority of cases with thymic LR presented with additional increasing tumor masses (33/34). All RTH patients (64/64) presented with isolated thymic growth.

Conclusion: Isolated thymic LR is very uncommon. CHL relapse should be suspected when increasing tumor masses are present in distant sites outside of the thymic area. Conversely, if regrowth of lymphoma in other sites can be excluded, isolated thymic mass after CTX likely represents RTH.

KEYWORDS
18F-FDG-PET, computed tomography, Hodgkin lymphoma, relapse, thymus, x-ray

1 | INTRODUCTION

The thymus is a lymphoid organ located in the upper and middle anterior mediastinum between sternum and heart. In small children, the thymus is very large and unproportionally big compared to the rest of the mediastinum.[1,2] After reaching its greatest weight in proportion to bodyweight before birth, the thymus continues to grow reaching its maximum absolute weight at puberty. The thymus subsequently decreases in size and weight with advancing age.[3] By early adulthood, the thymus is mostly replaced by fatty tissue.[4,5]

From late childhood, typically triangular or rhomboid appears on the thymus and shows a homogeneous parenchyma without any mass effects.[6,7] It has been suggested that thymic shape reliably separates normal from abnormal glands.[4]

The thymic tissue has a mixed soft tissue fatty structure in computed tomography (CT)[8] and magnetic resonance imaging (MRI) scans.[9] For that reason, it can be difficult to distinguish enlarged thymus glands from malignant lymphatic tissue.

Rebound thymic hyperplasia (RTH) is defined as an increase in size compared to prior MRI or CT imaging.[10]

It is a common phenomenon caused by different stress factors.[11] These include severe burning injuries, surgical interventions, tuberculosis, or treatment with steroids.[12] A recent study showed a correlation between RTH and novel coronavirus disease (COVID-19).[13] Atrophy of the thymus appears during the administration of chemotherapy (CTX), and regrowth is seen during the recovery phase after treatment.[14] Rebound appears within 1 year after cessation of CTX and persists for up to 4.5 years in adult patients.[12]

The incidence of thymic rebound after CTX in pediatric lymphoma patients varies between 44% and 67.7%.[10,15,16] On the other hand, more than two-thirds of pediatric Hodgkin lymphoma (HL) patients show mediastinal involvement.[17] Therefore, the differentiation of RTH

and lymphoma relapse (LR) seems to be a topic of clinical importance in pediatric HL.

HL accounts for 6% of childhood malignancies[18] and is the most commonly diagnosed cancer among adolescents aged 15–19.[19] In pediatric patients, malignant lymphomas are the most frequent malignancies in the upper and middle anterior mediastinum.[20] Primary or isolated mediastinal HL is rare.[20–22]

On initial staging, imaging features that differentiate between thymoma, lymphoma, thymic hyperplasia, and thymic cysts have been established for chest CT. Significant differences were shown for morphology, circumscription, fatty intercalation, presence of co-existing lymphadenopathy, overt pericardial invasion, and mass effect.[23] Positron emission tomography CT (PET-CT) was also able to distinguish between tumor entities using standardized uptake value (SUV) cutoffs.[15] HL lesions are regularly of focal and not diffuse appearance in fluorodeoxyglucose (^{18}F-FDG)-PET.[24,25] In MRI, chemical-shift imaging can be used for interpretation, although certain overlap exists in early adulthood.[26]

Discriminating between RTH and LR is even more challenging after CTX in pediatric HL patients. Thymic relapse in HL recurrence can be seen in up to 38%.[21] Imaging features common in RTH are a single, well-circumscribed mediastinal mass, a rhomboid, or triangular shape and of homogeneous density.[27]

1.1 | Aim of the study

Especially in pediatric or adolescent patients, previously published data about RTH contain only small cohorts or include patients with diagnoses other than HL.

The aim of this study is to identify possible morphologic parameters, which are able to differentiate between RTH and LR on follow-up imaging. These parameters should be based on a large pediatric HL population and be applicable to both MRI and CT imaging. This is important as misinterpretation of images might lead to unnecessary diagnostic procedures, including invasive biopsies. It may even result in inappropriate treatment decisions, for example, prolongation or change of CTX.

2 | MATERIALS AND METHODS

Data analyzed in our study were based on a prospective trial that was conducted by the European Network for Pediatric Hodgkin Lymphoma consortium (EuroNet-PHL). The EuroNet-PHL-C1 trial (EudraCT: 2006-000995-33; Clinicaltrial.gov: NCT00433459) recruited 2102 pediatric and adolescent classical Hodgkin lymphoma (CHL) patients between January 30, 2007 and January 29, 2013 (CHL as opposed to "nodular type of lymphocyte predominant Hodgkin lymphoma" is used whenever histology is specified, otherwise the inclusive term HL is used).[28] Imaging data (^{18}F-FDG-PET, CT, MRI) of 1752 patients were available to central review. As submitting follow-up imaging to central review was optional, we were able to include 291 patients with adequate follow-up imaging within 2 years after late response assessment (LRA).

The EuroNet-PHL-C1-trial was approved by the Ethics Committee of the University of Halle (Saale), Germany and the institutional review boards of the participating centers. It was conducted in accordance with the declaration of Helsinki. All patients and/or their guardians gave written informed consent to participate in the trial. Participation involved imaging procedures according to consensus protocols submitted to central review at diagnosis, after two cycles of CTX, and at the end of CTX prior to any consolidation radiotherapy. The institutional review board approved a retrospective imaging data analysis and waived the requirement for additional informed consent.

Patients from the EuroNet-PHL-C1 trial were included in our study if imaging from initial staging, restaging after the end of CTX (depending on the treatment group after two, four, or six cycles of CTX,[28] called LRA), and at least one further follow-up imaging (CT or MRI) within 2 years after LRA were available for central review. Patients with progression during primary therapy were excluded from the study.

In all patients with sufficient imaging data, thymic volume was measured at initial, LRA, and all follow-up imaging series within 2 years after the end of CTX (or after consolidation radiotherapy in cases with interim PET-positive disease) or up to the first relapse. In this timeline, the smallest thymic volume was identified for each patient. From that point, patients were screened for a significant increase in thymic volume. Significant increase of the minimal volume was defined as an increase of more than 10 mL and of more than 30%. Smaller increments were excluded to avoid error due to measurement inaccuracy[29] or imaging- and breathing-artifacts. Maximal thymic measures were obtained in three dimensions (anterior-posterior, transverse [Figure 1A], and cranio-caudal). As defined in the EuroNet-PHL-C1 trial imaging manual, thymic volume was calculated using the formula $V = (a^*b^*c)/2$.[30,31]

Thymic tissue structure was visually classified as homogeneous (Figure 1A) or inhomogeneous (Figure 1B). Areas with motion artifacts or beam hardening caused by high-concentrated contrast agents were excluded. Thymic shape was divided into three subtypes: triangular (Figure 1A), rhomboid, or irregular-bulky (Figure 1C).

According to Yarom et al., who described imaging characteristics of RTH,[12] data about size, structure, and shape were recorded. Additionally, we examined the presence of calcifications (Figure 1D)[32] and the occurrence of single (Figure 1A) or multiple masses in the thymic space.[16] The evaluation and image interpretation was done without knowledge of the clinical course by an experienced radiologist (Friedrich Christian Franke). In our multinational and multicenter approach, there was no standardized protocol for contrast agent dose or scanning delay. Unlike Zhen et al.,[33] we therefore did not measure the thymic density in Hounsfield units (HU) nor did we measure growth rates.

In all patients, clinical follow-up data (relapse dates, event-free survival, follow-up intervals, relapse sites) were obtained from the EuroNet-PHL-C1 trial database. In all patients with LR, an additional

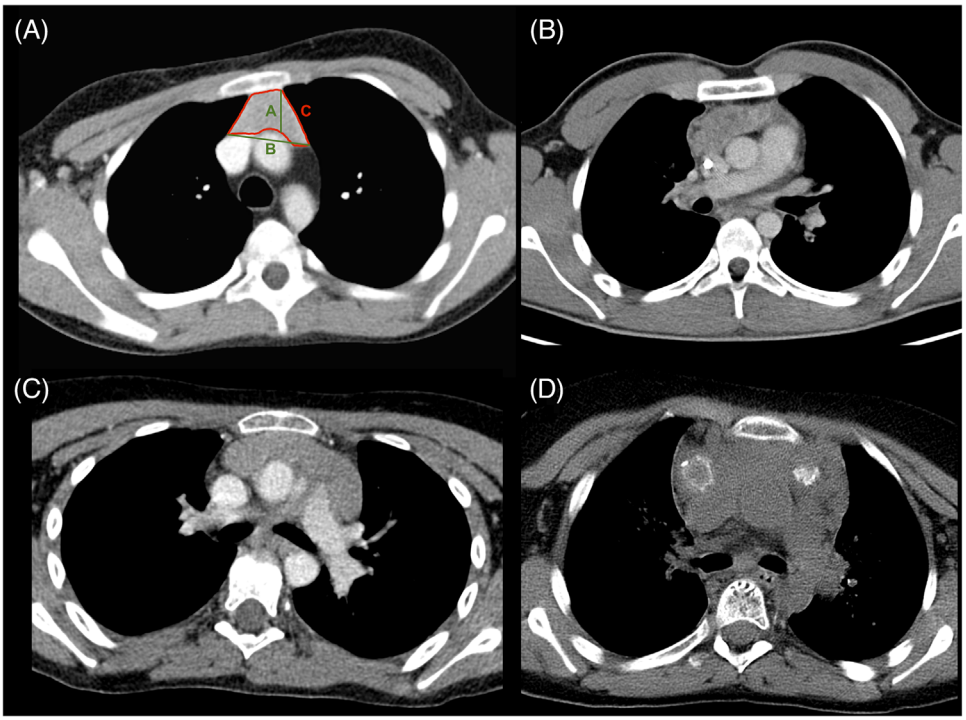

FIGURE 1 (A) Measurement of typical thymus in a homogenous thymus with triangular shape, (B) inhomogeneous thymus, (C) bulky-shaped thymus, (D) thymus with calcifications.

PET and morphological assessment of the thymus was re-evaluated in consensus by a radiologist (Dietrich Stoevesandt) and a nuclear physician (Lars Kurch), both experienced in the evaluation of pediatric HL. Thymic LR was defined as a positive biopsy with proof of CHL together with one or more focal FDG uptakes in the thymus that exceeded that of the liver.[24,34] The additional reassessment of the thymic region was done to rule out an alternative explanation for the increased PET uptake. A homogeneously thymic distribution of FDG uptake without focal lesions was not considered as thymic LR. Known unusual locations of thymic tissue like the neck or the superior mediastinum between the great thoracic vessels were evaluated in the same way.[35] Because of the multicenter approach, comparisons of SUV_{max} values and calculation of SUV_{max} cutoff values were not possible. Furthermore, there are no consistent quantitative cutoff value available in literature.[15,36,37]

Patients were split into three groups (Figure 2):

- Group 1 consisted of all patients with the final diagnosis of RTH. Patients included in this group had a follow-up of at least 18 months from regrowth without relapse.
- Group 2 consisted of all patients with the final diagnosis of thymic LR. To be included in this group, a histologically proven relapse had to occur within 2 months of regrowth. Also the combined PET and morphological assessment of the thymus described above had to be in concordance with thymic relapse.
- Group 3 consisted of all other patients with mediastinal regrowth that could not be included into either group 1 or 2, detailed reasons are listed in the results section.

Three groups were necessary, because only few patients underwent thymic biopsy. In most patients with progression on PET and/or CT/MRI, LR was diagnosed via lymph node biopsies from more readily accessible sites. In these cases, an additional thymic biopsy was not deemed ethical, making a third group necessary where diagnosis of thymic LR could neither be made nor excluded with sufficient certainty.

Statistical analysis was performed using R Version 4.0.2.

3 | RESULTS

The quality and quantity of imaging data differed, as CT and MRI scans were obtained in 133 different study sites in 14 European countries. There were different local imaging protocols, resulting in a variety of slice thickness, tube voltages, tube current, collimation, pitch, and application of contrast agent.

Out of 1752 enrolled patients participating in central review, we included 291 patients with adequate follow-up imaging within 2 years after LRA in our study; 121 (42%) were female. Mean age was 13.9 (interquartile range [IQR]: 12.5–16.3) years at the time of study enrollment, mean height was 161.8 cm, and mean weight 54.2 kg. CT and MRI on initial staging, LRA, or follow-up imaging were done in 77.1% of the patients, 22.9% only received CT imaging at all time points. The mean follow-up imaging time point was 236 days, with a standard deviation of 152 days.

The minimum thymic volume usually appeared at LRA (95.6%), only 4.1% reached the minimum volume on later follow-up imaging. A significant thymic regrowth within 2 years after the end of therapy was seen

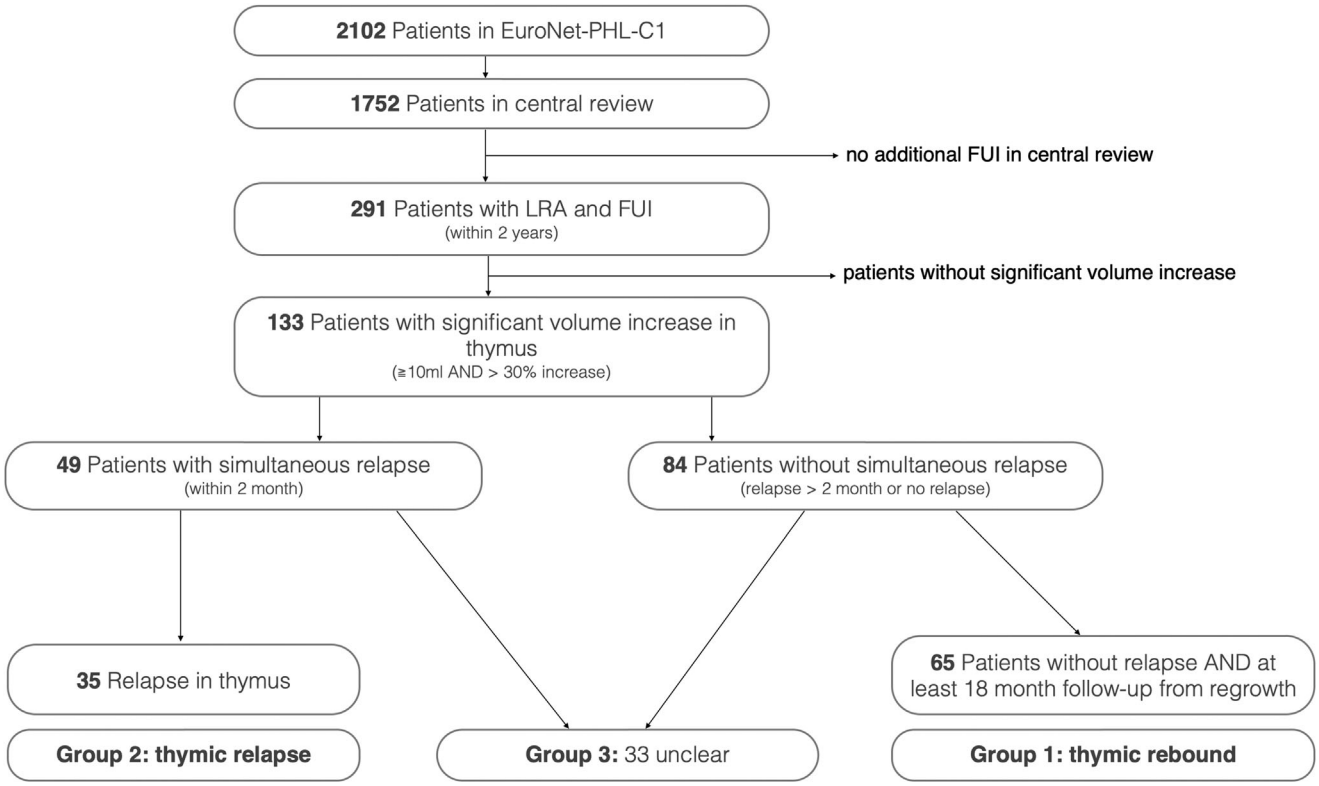

FIGURE 2 Study flowchart, process of selecting the final study population. Resulting in three groups, group 1 thymic rebound, group 2 thymic relapse, and group 3 all other patients.

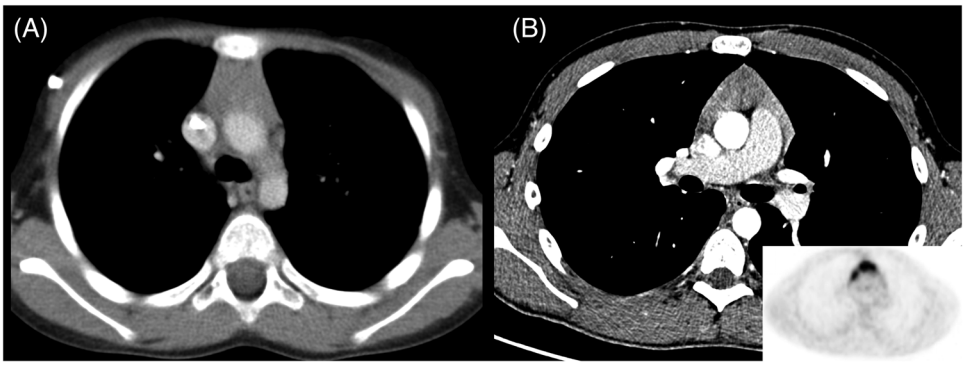

FIGURE 3 Rhomboid (A) and triangular (B) shapes both with homogeneous parenchyma without any mass effects in computed tomography (CT) appearance, less concerning for malignancy, of (A) rebound thymic hyperplasia (RTH) in a 4-year-old male patient but (B) thymic lymphoma relapse (LR) in a 15-year-old male patient. The corresponding PET in the lower right corner shows multifocal uptake.

in 45.7% of the cases (n = 133/291), and this cohort is likely enriched for thymic rebound.

Group 1 with the final diagnosis of thymic rebound included 64 patients (Figure 3A). Group 2 with the final diagnosis of thymic LR included 34 patients (Figure 3B). Group 3 with all patients who could not be included into either group 1 or 2 consisted of 35 patients. Reasons for the inclusion into this third group were follow-up less than 18 months after regrowth (n = 2), unclear status of thymic involvement on relapse PET staging (n = 1), LR without thymic relapse in combined PET and morphological imaging decision (n = 15), no simultaneous LR at the time of first documentation of regrowth but an LR within 2 years of follow-up (n = 17), and one patient with gray zone lymphoma as a secondary malignancy with resulting thymic regrowth. Group 3 was excluded from the assessment of imaging characteristics.

The following imaging characteristics of the thymus were assessed for their potential to differentiate between group 1 and 2.

Multiple masses (Figure 4A) in the thymic region were observed in 37.5% (n = 24/64) of the rebound group and in 67.6% (n = 23/34) of the

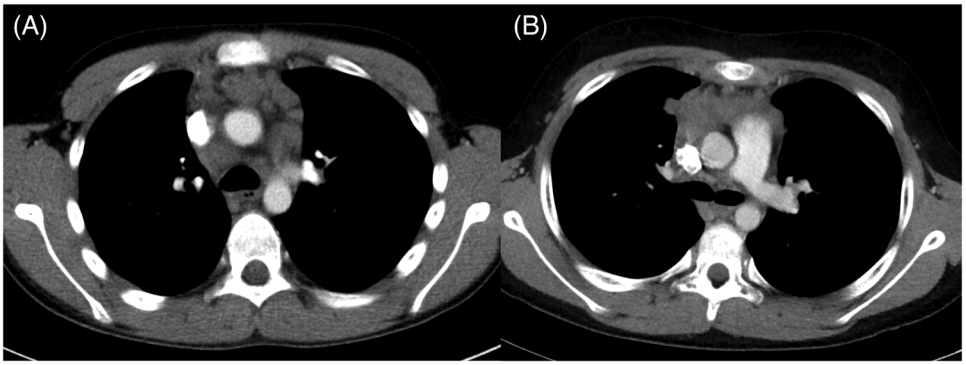

FIGURE 4 Computed tomography (CT) appearance with mass effect and inhomogeneous parenchyma concerning for malignancy of (A) rebound thymic hyperplasia (RTH) in a 15-year-old male patient, and (B) thymic lymphoma relapse (LR) in an 11-year-old male patient.

LR patients. While this finding was statistically significant (chi-square test, $p = .0012$), multiple masses were only 1.8 times more frequent in the thymic LR group. This criterion therefore cannot be used alone to reliably differentiate between the two groups.

Inhomogeneity (Figure 1B) of the thymic parenchyma at the time of regrowth was present in 46.9% ($n = 30/64$) of the RTH and 79.4% ($n = 27/34$) of the LR group. While statistically significant ($p = .0026$), this phenomenon alone was 1.7 times more likely to occur in the thymic LR group, but was not useful for an accurate distinction between both groups.

Rhomboid or triangular thymic shape (Figure 1A) occurred in 34.4% ($n = 22/64$) in the RTH group and in 20.6% ($n = 7/34$) in the LR group. Conversely, irregular bulky shape of the thymic volume (Figure 1C) was found in 65.6% and 79.4% of the two groups, respectively ($p = .22$).

Patients with appearance of calcifications (Figure 1D) in an anterior mediastinal mass were uncommon, 1.6% ($n = 1/64$) in the RTH and 2.9% ($n = 1/34$) in the thymic LR group. Therefore, there was no evidence of a significant correlation ($p = .874$) and, because of the rare occurrence of calcifications, this finding does not seem to have an impact on the differentiation between RTH and thymic LR.

Thymic involvement with thymic enlargement was frequently seen in patients at initial staging. This feature was present in 82.8% ($n = 53/64$) of the RTH group and in 91.2% ($n = 31/34$) in the thymic LR group ($p = .394$).

Isolated thymic LR in the absence of progressive tumor-suspicious lesions in other parts of the body was very uncommon. In groups 1 and 2 with either thymic rebound or LR isolated growth in the thymic space occurred in 65 patients of whom 98.4% ($n = 64/65$) had RTH and only 1.5% ($n = 1/65$) suffered thymic LR ($p < .001$). This patient was a 15-year-old male with a very late thymic growth after more than 1 year (387 days) (Figure 5). In contrast, all patients ($n = 34/34$) with thymic regrowth and suspicion of progression in one or more extrathymic regions suffered thymic relapse.

As this was a retrospective study, there were no defined control dates, we therefore were unable to calculate growth rates or the point in time of the maximum size in thymic LR or rebound.

Mean time from LRA to maximum thymic volume was 199 days ($\pm$140 days) but differed significantly between the LR (240 $\pm$ 156 days) and RTH (158 $\pm$ 110 days) groups ($p = .0092$).

PET-CT data on regrowth were available in 46 patients, 15 from group 1 and 31 from group 2. Focal ^{18}F-FDG-PET uptake (Figure 3B) was only seen in patients from group 2 (93.5%, 29/31), but in no patient from the RTH group ($p < .00001$). Patients from the RTH group showed mild to markedly increased but homogeneously thymic ^{18}F-FDG-PET uptake.

4 | DISCUSSION/CONCLUSION

There is a need for imaging parameters to differentiate RTH from thymic LR because of its diagnostic and therapeutic consequences. Today uncertainties about rebound after CTX still lead to invasive interventions or unnecessary treatment intensifications.[38] This distinction may be particularly important in pediatric CHL where the majority of patients show mediastinal involvement,[17] and thymic rebound may be more common than in adult lymphoma patients. It appears important to study this topic in a homogeneous population of CHL only.

Although thymic regrowth was present in 45.7% of the cases ($n = 133/291$), we cannot calculate the incidence of RTH because there were no defined time points for central review imaging evaluation in the EuroNet-PHL-C1-trial, and sending imaging after the end of CTX was voluntary. Therefore, patients with thymic regrowth may be enriched or a larger number of benign appearing RTH patients may not have been sent to central review.

In our study of pediatric CHL, we failed to identify a single criterion such as shape, size, structure, or morphology of the thymus in standard CT and MRI scans that reliably discriminates RTH from thymic LR when a new or growing mass in the anterior mediastinum is seen after CTX. Only one case of isolated thymic LR was seen in our series, and the vast majority of thymic LR occurred as part of more widespread extrathymic progression of CHL. Therefore, whole-body imaging to screen for distant relapses seems a clinically meaningful way of discriminating between RTH and LR.

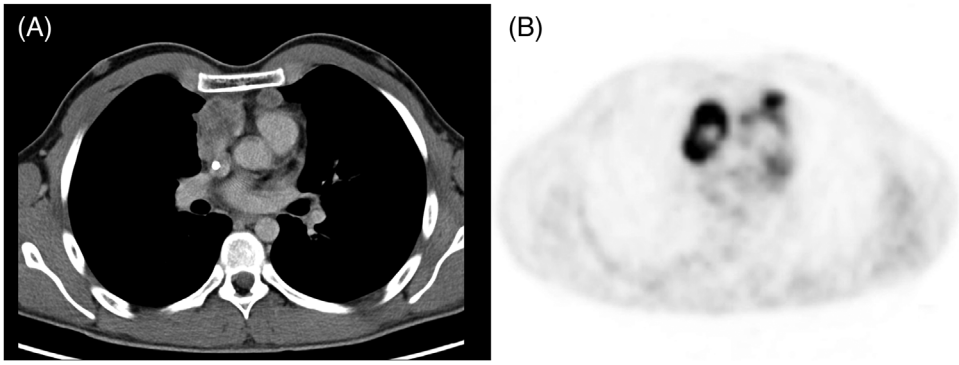

FIGURE 5 Isolated thymic lymphoma relapse (LR) in a 15-year-old male patient after 387 days.

Few studies regarding this topic have been published. They were based upon a limited number of study participants, case reports, or included other histological entities than HL. In the study of Fouda et al.,[16] for example, only four patients with thymic rebound in HL were included. Tian et al.[27] reported one patient with CHL (in addition with 14 lymphocyte-predominant HL), and Chen et al.[10] investigated eight HL patients. In summary, this results in a total of only 25 HL patients in three studies, CHL and lymphocyte-predominant HL combined. In contrast, our study, which recruited CHL patients from a prospective trial with standardized imaging and treatment and long-term follow-up, allows a more reliable approach to this clinically important distinction.

Other approaches relying on functional imaging data have been suggested to allow differentiation between RTH and thymic relapse in lymphoma patients. For instance, in pediatric patients, thymic ^{18}F-FDG uptake increases after completion of CTX,[36] a maximum standard uptake value (SUV) of 3.4 or higher in thymic regrowth has been suggested to be a strong predictor of LR.[15] This study by Gawande et al. however included only five patients with a thymic LR, two patients with HL, and three with non-Hodgkin lymphoma (NHL). The utility of a cut-off SUV of 3.4 was also questioned by Jerushalmi et al., who found higher mean SUVs (mean SUV_{max} of 3.73 ± 1.22) in ^{18}F-FDG-PET of the physiologic thymus on follow-up imaging in patients younger than 40 years.[35]

Priola et al. even reported SUV_{max} higher than 4.0 in 44% of patients.[37]

Unfortunately, we were not able to use FDG-PET data from our patients, as SUV_{max} cutoff analysis requires that PET studies are performed under comparable conditions, which is impossible in a multicenter trial. Routine use of PET-CT or PET-MRI in follow-up imaging would increase false-positive PET findings in general, relating to other areas than the thymus, and would also increase radiation dose compared to CT or MRI alone. Therefore, PET imaging should be used frugally, and simpler tools to discriminate RTH and thymic LR may be preferred. However, focal ^{18}F-FDG-PET uptake is a strong indicator of thymic relapse in our cohort.

From the above-mentioned studies, there seem to be no reliable parameters to securely differentiate rebound from thymic LR by CT-morphology alone. Tian et al. examined 52 pediatric lymphoma patients with CT who developed RTH following CTX. The absence of LR, like in our study, was confirmed with long-term review and follow-up and serial imaging. However, Tian et al. only included one patient with CHL. The authors found no characteristic shape or density of RTH: 81% (n = 42/52) showed trapezoidal or triangular shapes and were well-circumscribed; 19% (n = 10/52) manifested diffuse shapes and were ill-circumscribed; 81% (n = 42/52) showed homogeneous density, although all of the 52 cases presented with a single mediastinal mass.[27] This corresponds with our observation that RTH does not have a consistent shape that would give promise to allow differentiation from thymic LR.

Zhen et al. also studied the morphology of RTH, but similarly failed to include a comparable group with thymic LR. They described RTH in CT as mostly diffuse enlarged thymic parenchymatous tissues that maintained normal thymic morphology. The mean volume of the thymic mass was 19.2 cm^3.[33] Zhen et al. report CT values of 36.72 ± 9.48 HU in RTH that increased by 5.56 ± 2.62 HU in contrast enhancement. As described above, the assessment of HU and volumes was not applicable in our study.

Whether imaging data from MRI more accurately differentiates RTH from thymic LR is also unclear, especially in pediatric patients. In their meta-analysis, Li et al. stated that the diagnostic accuracy of MRI is superior to CT in detecting rebound with a diagnostic accuracy of 97.9% versus 84.0%.[39] The authors do not state how many pediatric patients were included, and this meta-analysis contains adult-only data of the Priola et al. study.[26] No comparison of the relative merit of the two methods in differentiating RTH and thymic LR was given. In another study, Priola et al. showed that diffusion-weighted MRI is a valid method to distinguish lymphoma from normal thymus in untreated patients, but no conclusion can be drawn whether this method can be applied to distinguish LR from RTH.[40] MRI chemical-shift imaging may be considered a possible diagnostic alternative to differentiate RTH and thymic LR, as MRI is noninvasive. Data on such approaches are still scarce,[26,41,42] and the published studies have limited relevance to pediatric CHL. One study contained only two lymphoma patients (of 18 patients with malignancies),[41] another compared RTH to other diseases like myasthenia gravis,[42] and a third study only included patients older than 18 years.[26] MRI and especially chemical-shifting imaging represent interesting approaches, but due

to the inhomogeneity of the study protocols in our international and multicenter trial, such detailed MRI analyses are not always feasible.

Isolated Hodgkin disease of the thymus is uncommon on initial staging.[21,22] From our study data, it can be concluded that an isolated thymic LR is also very uncommon, coinciding with Heron's findings published in 1988 with mainly adult patients.[21] The only isolated thymic LR occurred very late after more than 12 months (387 days) (Figure 5), which is uncommonly late for RTH. The mean time from LRA to the diagnosis of RTH in our collective was 5 months after the end of therapy. This is comparable to the time intervals found by Yarom et al. with a mean interval of 5 months.,[12] Gawande et al. of 10 months,[15] and Fouda et al. of 4 months.[16]

Recurrent CHL of the thymus should be suspected mainly when there are morphologic signs of progression not only in the thymic space but in other locations, such as extrathymic lymph node areas. On the other hand, if regrowth of lymph nodes or masses in other sites can be excluded, isolated growth of the thymus after CTX should be evaluated as a rebound phenomenon, a physiological reaction following stress induced by CTX.

In conclusion, we were able to show that isolated thymic enlargement without signs of CHL progression in other sites of the body most likely represents rebound, eliminating the need for additional diagnostic imaging or even biopsy in most cases. Knowledge of RTH and its frequent occurrence is important to avoid superfluous or redundant diagnostic procedures, additional CTX or radiotherapy, or even surgical interventions.

4.1 | Limitations

Our data were based on a multicenter study. Therefore, CT imaging protocols and parameters such as slice thickness, application of contrast agent (e.g., concentration and delay times) differed. We therefore could not include HU density in our assessed parameters.

This study is not designed to calculate the incidence of RTH during follow-up because of selection bias. All cases in the study were assessed by central review directly after CTX, but submitting follow-up imaging to central review was optional, mainly used as service of second opinion in cases with unclear findings. Therefore, cases with relapse and other diagnostic dilemmas are probably enriched in this dataset.

There was no histopathological proof of thymic hyperplasia in cases classified as RTH. Also, in most cases classified as thymic LR, the biopsy was done in extrathymic locations and bioptical proof of thymic involvement was not possible due to ethical and diagnostic concerns of performing needle biopsy in the anterior mediastinum in CHL.[43]

4.2 | Take-home message

In pediatric and adolescent HL patients, LR rarely manifests with an isolated relapse in the thymic space. Furthermore, as there is no simple imaging feature that can distinguish between thymic rebound and thymic LR, in most cases isolated thymic enlargement can be considered to be RTH. If thymic regrowth appears after more than 1 year, ^{18}F-FDG-PET to detect focal thymic uptake and targeted biopsies as the gold standard for diagnosis of relapse should be considered.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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