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ORIGINAL ARTICLE

Volume and attenuation computed tomography measurements for interim evaluation of Hodgkin and follicular lymphoma as an additional surrogate parameter for more confident response monitoring: a pilot study

Daniel Spira[a], Martin Sökler[b], Wichard Vogel[b], Sarah Löffler[a], Sven Michael Spira[c], Harald Brodoefel[a], Michael Fenchel[a] and Marius Horger[a]

[a]Department of Diagnostic and Interventional Radiology, Eberhard-Karls-University, Hoppe-Seyler-Strasse 3, 72076 Tübingen, Germany; [b]Department of Oncology and Hematology, Eberhard-Karls-University, Otfried-Müller-Strasse 10, 72076 Tübingen, Germany; [c]Finance Department, HEC Paris, 1, rue de la Libération, 78350 Jouy en Josas, France

Corresponding address: Daniel Spira, MD, Department of Diagnostic and Interventional Radiology, Eberhard-Karls-University, Hoppe-Seyler-Strasse 3, 72076 Tübingen, Germany.
Email: daniel_spira@yahoo.de

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Abstract

Purpose: To retrospectively determine the potential role of additional computed tomography (CT) attenuation measurements for interim response evaluation in residual masses of patients with Hodgkin disease (HD) and follicular non-Hodgkin lymphoma (NHL). **Materials and methods:** In this retrospective study, 39 patients with HD and 35 patients with NHL presented with residual masses at mid-treatment CT (after 2–4 cycles of chemotherapy) and were assessed via contrast-enhanced CT at baseline, mid-treatment and post-treatment. Volume was recorded as whole-tumour volume. A tumour attenuation ratio (TAR) was calculated as the quotient of attenuation between tumour and muscle at the respective point in time versus baseline. The standard deviation of attenuation values within the tumour volume was recorded to estimate tumour heterogeneity. Results were correlated with relapse-free survival determined at a minimum of 12 months after end-treatment CT. **Results:** Tumour volume and TAR at interim versus baseline control were significantly reduced in responders compared with non-responders, even after controlling for age, stage, treatment regimen, and baseline tumour volume. No significant differences with respect to the standard deviation of attenuation values within the tumour volumes (tumour heterogeneity) were observed. The volume and attenuation CT (VACT) criteria yielded the highest sensitivities and specificities for the identification of non-response at a threshold of a >20% increase in volume and an increase in TAR at interim control, i.e. 88% (NHL 80%, HD 100%) and 98% (NHL 97%, HD 100%), respectively. The negative predictive values reached by VACT analysis were ≥97%, according to both parameters. **Conclusion:** Mid-treatment response assessment of residual masses in patients with HD and NHL using VACT may aid in the risk stratification as an additional surrogate parameter.

Keywords: *Hodgkin disease; follicular lymphoma; volume and attenuation CT; VACT; interim response evaluation.*

Introduction

Computed tomography (CT) morphologic assessment of treatment response in lymphoma largely relies on evaluation of tumour size. However, residual and even bulky masses at mid-treatment or after completion of therapy are frequent in 2 common lymphoma entities: Hodgkin disease (HD) and follicular non-Hodgkin lymphoma (NHL) occurring in up to 64% of patients; only 18% of these patients will eventually relapse[1,2]. Therefore,

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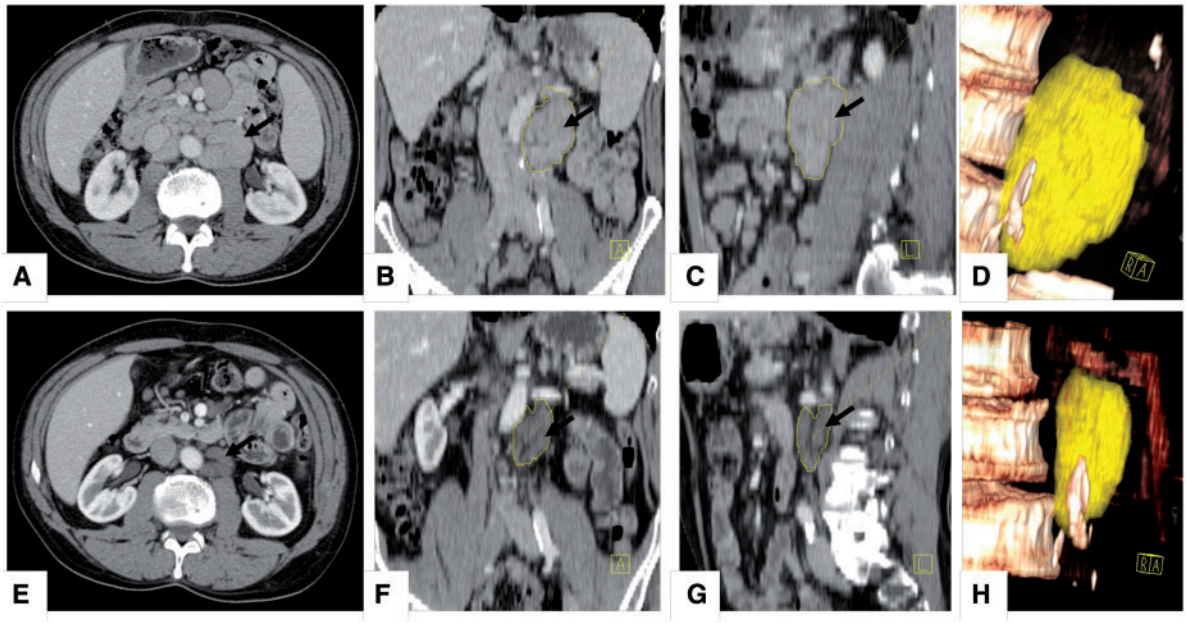

Figure 1 **A 65-year-old male responder with grade 3 follicular lymphoma. At baseline CECT (A–D) the left paraaortic lymphoma (arrow) measured 70 ml with a mean tumour density of 80 ± 21 HU. Axial (A), reconstructed coronal (B), reconstructed sagittal (C), as well as three-dimensional reconstructed views (D) are presented. Two months later, after 3 cycles of R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone) (E–H) a residual mass (arrow) is demonstrated with a volume of 22 ml and mean tumour density of 17 ± 26 HU. Axial (E), reconstructed coronal (F), reconstructed sagittal (G), as well as three-dimensional reconstructed views (H) are presented. Note the decrease in tumour attenuation. No relapse occurred during 12-month follow-up.**

assessment of additional parameters characterizing a residual mass during treatment of lymphoma remains one of the most challenging aspects in the evaluation of response to therapy. Early salvage therapy or hematopoietic stem cell transplantation at the time of minimal disease in patients with persistent vital tumour could be beneficial in these patients[3,4]. On the other hand, risk-adapted strategies with reduced treatment intensity in early-stage lymphoma are currently discussed[5]. Until now, no reliable CT morphologic criteria have allowed interim differentiation between responding and non-responding tumours. Risk stratification of patients with lymphoma is enhanced to some degree by the use of fluorodeoxyglucose (FDG)-positron emission tomography (PET) and/or PET/CT[6–8], as [^{18}F]FDG-PET at mid-treatment or after completion of therapy is predictive of progression-free survival and overall survival[9]. An intention to cure is valid for HD, however it is often not for NHL. Knowledge about the short-term risk of relapse and a possible need for additional radiation therapy in selected patients is of interest in both types of lymphoma.

The latest version of Revised Response Criteria for Malignant Lymphoma according to Cheson et al. is based on measurements of long- and short-axis tumour size, [^{18}F]FDG-PET, immunohistochemistry, and flow cytometry[10]. However, as cell density and vascularization of tumour masses is reflected by CT attenuation, and as chemotherapy leads to a reduction in cell mass and blood vessels, a treatment response should cause changes in attenuation on contrast-enhanced CT (CECT. Therefore, supplementary data that are already collected in every standard CT examination such as attenuation and contrast enhancement may improve response assessment.

As therapy-induced attenuation changes on CECT are not accounted for by the Cheson criteria[10], we set out to retrospectively evaluate residual masses in patients with NHL and HD at mid-treatment (interim) control with respect to dynamics in volume and attenuation (Figs. 1 and 2).

Materials and methods

Patients

The local institutional review board approved this retrospective study. A search of our institution's electronic medical record database from 2002 to 2009 was performed for patients who were treated for HD or NHL. Patients treated for HD and those who received treatment for NHL totalled 119 and 110, respectively. Patients who underwent non-enhanced CT or those who did not undergo mid-treatment CT control and

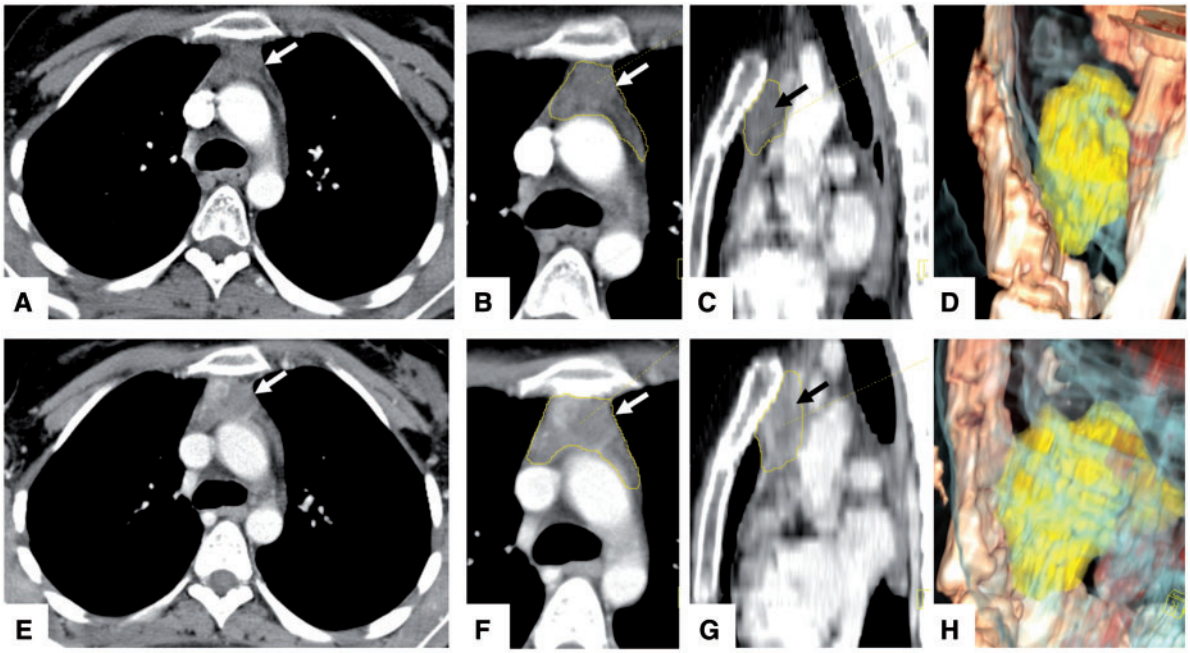

Figure 2 **A 20-year-old female responder with HD. At baseline CECT (A–D) the mediastinal lymphoma (arrow) measured 9 ml with a mean tumour density of 36 ± 18 HU. Axial (A), reconstructed axial (B), reconstructed sagittal (C), as well as three-dimensional reconstructed views (D) are presented. Three months later, after 2 cycles of DHAP (dexamethasone, cytarabine, cisplatin) (E–H) disease progression (arrow) is demonstrated with a tumour volume of 21 ml and a mean tumour density of 65 ± 30 HU. Axial (E), reconstructed axial (F), reconstructed sagittal (G), as well as three-dimensional reconstructed views (H) are presented. Note the increase in tumour attenuation.**

those without residual masses after completion of therapy were excluded from the study. A total of 39 patients with HD and 35 patients with NHL presented with residual masses that were assessed via CECT at mid-treatment (after 2–4 cycles of therapy) and were included in the analysis (Table 1).

CT examination time points

For each patient, CECT examinations were assessed before treatment initiation (baseline), during treatment (mid-treatment) as well as after completion of therapy (end-treatment) and also during follow-up (at least 12 months post-treatment) in order to exclude relapsing disease. Mid-treatment CECT examinations were performed at a median of 2 months (range 1–5 months) after baseline in patients with HD, and at a median of 2 months (range 1–4 months) after baseline in patients with NHL.

Imaging protocol

Images were acquired through CECT which was conducted on multidetector CT scanners (Sensation 4/16/64, Siemens Healthcare, Erlangen, Germany) and included intravenous administration of 120 ml of non-ionic iodinated contrast material (360 mg/ml iopromide [Ultravist, Bayer Vital, Leverkusen, Germany]) with an injection rate of 2.5 ml/s in an antecubital vein followed

Table 1 ***Patient characteristics***

	NHL		HD	
No. of cases	35		39	
Age (years)	56 (range 38–75)		37 (range 18–84)	
Sex (female/male)	17/18		16/23	
Histology	Grade I–II	29	Nodular sclerosis	29
	Grade III	6	Mixed cellularity	7
	Grade IV	0	Lymphocyte-rich	2
			Lymphocyte-depleted	1
Ann Arbor stage				
I	1		3	
II	4		14	
III	16		13	
IV	14		9	
Treatment regimens	R-CHOP	23	BEACOPP	25
	R-Benda	5	ABVD	11
	R-VIPE	3	DHAP	2
	VACOP-B	2	Gemcitabine	1
	IF radiation	1		
	R-FCM	1		

Abbreviations: ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPP, cyclophosphamide, etoposide, adriamycin, vincristine, bleomycin, prednisolone; DHAP = dexamethasone, cytarabine, cisplatin; IF radiation, involved field radiation; R-Benda, rituximab + bendamustine; R-CHOP, rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone; R-FCM, rituximab, fludarabine, mitoxantrone, cyclophosphamide; R-VIPE, rituximab, vincristine, ifosfamide, cisplatin, etoposide; VACOP-B, doxorubicin, cyclophosphamide, vincristine, bleomycin, etoposide.

by a saline flush of 50 ml NaCl at 2.5 ml/s. Contrast material was administered by using a dual-head pump injector (Stellant, Medtron, Saarbruecken, Germany). Chest images were obtained 30 s after intravenous contrast application and abdominal/pelvic imaging was performed 70 s after injection. Scan parameters included 0.6 mm collimation, 0.5 s rotation time with 0.6 mm increments. Images were obtained at 120 kV for neck, thorax and abdomen, respectively.

Imaging analysis

Images were analysed by a consensus of 2 radiologists (MH, DS) with extensive experience in reading CT scans of oncologic patients, who were unaware of the clinical and follow-up data. The course of all lymphoma manifestations was evaluated on a whole-body CT. Residual masses were defined according to the latest version of Revised Response Criteria for Malignant Lymphoma (Cheson et al.)[10].

Patients were categorized accordingly into partial remission (PR), stable disease (SD), relapsed disease/progressive disease (PD). A total of 47 residual masses in patients with HD and 44 masses in patients with NHL were observed. The main residual mass of each patient was selected and followed (39 residua in patients with HD (i.e. 83% of all HD residues), and 35 in patients with NHL (i.e. 79% of NHL residues)). In patients with more than one residuum the largest tumour bulk was chosen for follow-up. However, more than 2 residua occurred only rarely. Images of all patients were evaluated retrospectively just before initiation of chemotherapy, during and after completion of treatment. The inactivity of residual masses was confirmed by unchanged or regressive size on follow-up CT scans. The location of residual masses was assessed and compared in both disease groups. Changes in tumour volume were determined by manual placement of a volume of interest (VOI) on the tumour (with the Siemens Oncology/Volumetry tool on a dedicated workstation). Consecutive whole-tumour measurement of the residual mass at the respective point in time (baseline, mid-, end-, or post-treatment) was divided by the volume at baseline. In residual masses encasing blood vessels, care was taken to exclude vascular structures from the VOI. Mean attenuation of the entire residual masses was assessed by direct measurements of Hounsfield units within the VOI. The standard deviation of attenuation values within the tumour volume was recorded to estimate tumour heterogeneity. In addition, attenuation of muscle tissue at the same body height as the residual mass was measured to correct for differences in cardiovascular circulation time. During follow-up, measurements were performed in the same muscle at the same body height to avoid inter-muscular attenuation differences due to variable fat content and vascularization. A tumour attenuation ratio (TAR) was calculated as the quotient of attenuation between tumour and muscle at the respective point in time versus baseline.

Statistical analysis

Values are expressed as median and range or mean percentage as appropriate. An ordinary least squares (OLS) regression was used for group comparison in order to consider control variables (i.e. age, stage, treatment regimen, baseline tumour volume) (software: Stata 10.0; StataCorp LP). An F-test was applied to test for joint significance of variables. A paired t-test was used for within-group comparisons. p values <0.05 were considered as statistically significant. Sensitivity, specificity, negative and positive predictive values are displayed for the respective criteria.

Results

Location of residual masses

Thoracic masses were observed as the dominant residuum in 27/39 patients (69%) with HD but only in 2/35 patients (6%) with NHL. In contrast, abdominal residual masses were assessed in 7/39 patients (18%) with HD and 30/35 patients (86%) with NHL. Dominant residua in the neck or axilla only occurred in a minority of patients in both disease groups (5/39 (13%) with HD, 3/35 (9%) with NHL).

Tumour volume

An OLS regression showed that changes in volume (Table 2) differed significantly among responders and non-responders and that this difference remained significant after controlling for age, stage, treatment regimen, and baseline tumour volume ($p<0.05$ for all groups, i.e. NHL, HD, and both lymphomas combined). Furthermore, the coefficients on the control variables were individually and jointly insignificant in all regressions. Ninety-eight percent of all patients with lymphoma who remained in remission for $\geq$12 months showed a decrease in volume of >20% at interim control. A decrease in volume of >50% occurred in 90% and 100% of patients with NHL and HD, respectively (Table 2). Conversely, 7/8 (88%) patients with non-response to treatment (5 with NHL and 3 with HD) showed an increase in volume of >20%. At a threshold of >20% increase in volume at interim control the sensitivity and specificity for PD in all lymphoma patients (NHL+HD) reached 88% and 98%, respectively (Table 4). However, 2/66 patients (3%) with response to treatment (1 with HD and 1 with NHL) initially responded to chemotherapy with masses decreasing in volume and attenuation but relapsed at 3 and 6 months post-treatment, respectively (Tables 2 and 3).

Tumour attenuation

An OLS regression showed that TAR was significantly reduced in responders compared with non-responders and that this difference remained significant after

Table 2 Response evaluation at interim control: tumour volume

Disease status	Mean % change in volume	% of patients with mass showing				No. of patients
		>90% decrease in volume	>70% decrease in volume	>50% decrease in volume	>20% increase in volume	
NHL: Remission for ≥12 months	−70	14	69	90	3	29
HD: Remission for ≥12 months	−78	9	80	100	0	35
NHL: Progression after ≤12 months	+89	0	0	17	67	6
HD: Progression after ≤12 months	+63	0	0	25	75	4

Table 3 Response evaluation at interim control: TAR

Disease status	Mean % change in TAR	% of patients with mass showing				No. of patients
		>50% decrease in TAR	>30% decrease in TAR	>15% decrease in TAR	>0% increase in TAR	
NHL: Remission for ≥12 months	−35	34	59	79	10	29
HD: Remission for ≥12 months	−36	29	60	80	0	35
NHL: Progression after ≤12 months	+62	17	17	17	83	6
HD: Progression after ≤12 months	+27	0	0	0	75	4

controlling for age, stage, treatment regimen, and baseline tumour volume (Table 3; $p < 0.05$ for all groups, i.e. NHL, HD, and both lymphomas combined). Furthermore, the coefficients on the control variables were individually and jointly insignificant in all regressions. A decrease in TAR of >15% was noted in 79% and 80% of NHL and HD patients that remained in remission for ≥12 months, respectively (Table 3). In contrast, all 8 (100%) patients with non-response to treatment (5 with NHL and 3 with HD) showed an increase in TAR at interim control. An increase in TAR was seen in only 3/66 patients (5%) with response to treatment (both with NHL). To estimate tumour heterogeneity, the average standard deviations of attenuation values within the tumour volumes were recorded as 22 HU at baseline versus 28 HU at interim for HD, and as 21 HU at baseline versus 27 HU at interim for NHL. An OLS regression revealed no significant differences between responders and non-responders ($p > 0.05$, respectively). Accordingly, a paired t-test showed no significant differences between baseline and interim control either ($p > 0.05$, respectively). With the criterion of an increase in TAR at interim control, the sensitivity and specificity for PD in all lymphoma patients (NHL+HD) reached 100% and 95%, respectively (Table 4). Negative and positive predictive values were 100% and 72%, respectively (Table 4).

Table 4 Interim response evaluation using both size and CT TAR

	Criterion for PD	Sensitivity	Specificity	NPV	PPV
NHL					
Tumour size	>1.20	0.80	0.97	0.97	0.80
TAR	>1.00	1.00	0.90	1.00	0.63
HD					
Tumour size	>1.20	1.00	1.00	1.00	1.00
TAR	>1.00	1.00	1.00	1.00	1.00
Overall					
Tumour size	>1.20	0.88	0.98	0.98	0.88
TAR	>1.00	1.00	0.95	1.00	0.72

Residual masses in responders and non-responders were compared. Measurements were undertaken at mid-treatment (interim) on a total of 74 patients (NHL $n = 35$, HD $n = 39$). Changes in tumour size were determined by whole-tumour measurement of the residual mass at interim control divided by the volume at baseline. TAR was measured as the quotient of attenuation between tumour and muscle at interim control divided by the quotient of attenuation between tumour and muscle at baseline ($\text{Control}_{\text{mass/muscle}}/\text{Baseline}_{\text{mass/muscle}}$). The criterion for PD indicates the threshold above which a disease progression was recorded. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) are displayed.

Discordance of volume and CT attenuation

Dynamics in volume and attenuation of masses diverged in 5/74 patients (7%). One in 8 patients (13%) with non-response to treatment proved false-negative according to volume measurements due to a decrease in volume of 48%. An increase in TAR disclosed a disease progression in this patient, which was confirmed by the consecutive disease course. Conversely, 1/64 patients (2%) remaining in remission for ≥12 months proved false-positive according to volume measurements showing an increase in volume of 100% at interim control accompanied by a decrease in TAR of 28%. False-positive results according to attenuation measurements (increase in TAR) occurred in 3/35 patients (9%) with NHL and 0/39 patients (0%) with HD.

Combined assessment of volume and CT attenuation for interim response evaluation

The combination of a decrease in volume and attenuation ratio indicated a response in 60/60 patients (100%). An increase in volume and a decrease in TAR occurred in only 1 patient who was disclosed as a responder. All 8/8 patients (100%) who demonstrated an increase in both volume and TAR were non-responders. The combination of a decrease in volume but an increase in TAR proved to be inconclusive, being recorded in 1 non-responder and 3 responders.

Discussion

Lymphoma accounts for 5–6% of malignancy in adults and about 10% of all childhood cancers[11]. They are solid tumours of lymphoid cells and subdivided into HD and NHL. HD shows a bimodal peak, the first occurring in the third decade of life and the second between 65 and 75 years of age. NHL is a disease of the elderly with an increasing incidence over the age of 50 years[12].

The standard staging examinations used for most patients with lymphoma include chest radiography, CT of the chest, abdomen, pelvis, and neck, complete blood cell count, erythrocyte sedimentation rate, electrolyte evaluation, renal and liver function tests, serum albumin and serum lactate dehydrogenase measurements. HD with its preference for the neck (60–80%) and thorax (60–85%) affects the mediastinum in the pre-vascular and para-tracheal regions (84% of patients), but hilar (28%) and subcarinal node involvement (22%) is also frequently noted[13]. In contrast, mesenteric lymph nodes are involved in more than 50% of patients with NHL and <5% of patients with HD[11]. These differences with respect to incidence of regional nodal involvement are well represented in our patient group: 69% of patients with HD showing thoracic residua and 86% of NHL patients presenting residual abdominal masses.

Currently, the challenge in lymphoma therapy is to improve cure rates (in the case of HD) or relapse-free survival (in NHL) while minimizing the likelihood of long-term adverse effects. Therefore, attempts have been made to develop risk-adapted radio-/chemotherapy protocols[4,9,14,15]. Response assessment by [^{18}F]FDG-PET and magnetic resonance imaging may help to identify the group of patients in whom therapy regimens can be reduced without exposing the patient to the risk of relapse or disease progression[16]. A meta-analysis by Zijlstra et al.[17] quoted pooled sensitivity and specificity of [^{18}F]FDG-PET for detection of residual disease after completion of first-line therapy 84% (95% CI 71–92%) and 90% (95% CI 84–94%), respectively, for HD and 72% (95% CI 61–82%) and 100% (95% CI 97–100%), respectively, for NHL.

It was shown that gadolinium enhancement of mediastinal lymphoma masses decreased markedly during and after treatment in responders, but not in non-responders[18]. Furthermore, a decrease in attenuation on CECT was observed after targeted therapy in renal cell carcinoma and gastrointestinal stromal tumour, reflecting depletion in tumour cell population and necrosis[19–21]. Thus, we aimed to compile cutoff values concerning volume and CT attenuation dynamics at interim control of residual masses to maximize the accuracy of evaluation and risk stratification. In this study, the vast majority of masses in lymphoma patients who remained in remission for $\geq$12 months showed a decrease in volume of >10% accompanied by a decrease in TAR of >15%. Conversely, an increase in volume of >20% and an increase in TAR was noted in 7/8 patients (88%) with non-response to treatment. Therefore, criteria for disease progression (PD) at interim control were set at an increase in volume of >20% and an increase in TAR and criteria for response to treatment were set at a decrease in volume of >10% and a decrease in TAR of >15%. An increase in TAR was observed in 5% of non-relapsing lymphoma patients at interim analysis. Therefore, an early rise in TAR during treatment is not necessarily an ominous sign in HD and NHL in cases where it is not accompanied by significant tumour growth, but may rather represent a reactive hyper-vascularization and hyper-perfusion of treated masses due to temporary inflammation[18]. This is especially true for the early post-treatment phase, i.e. within the first 6 months after therapy[22]. Interim control of both volume and attenuation failed to predict early relapse ($\leq$12 months after end-treatment control) in 2 patients with treatment response. The sensitivities and specificities of volume, attenuation and combined criteria did not significantly differ from each other (Table 4 and Results section). However, in selected cases where the size of residual masses remains relatively stable or even increases, a significant decline in TAR may point to a remission. We feel that the TAR should be considered in the evaluation of residual masses. Only rarely did dynamics in volume and attenuation of masses diverge. In these patients further clarification of disease status needs to be performed by a supplementary short-term follow-up CT control or by [^{18}F]FDG-PET.

This study has several limitations that need to be discussed. First, 2 common lymphoma entities with different tumour biology, prognosis and chemotherapy regimens were evaluated. Whether these results can be extended to other types of lymphomas is not known. Second, differences in circulation time lead to minor variations in contrast phases of the residual masses. Furthermore, masses in the thorax were assessed during late arterial phase, whereas masses in the abdomen and neck were measured at portal venous phase, which complicates a direct comparison of residua in both regions. However, we mitigated these differences by a normalization of

tumour attenuation values to muscle, a strictly intraindividual comparison of values and the use of a standardized CT protocol. Histologic or functional verification of the response status would have been meaningful adjuncts to this study. As no simultaneous or consecutive PET examinations were available, the responders were identified by relapse-free survival on follow-up CT examinations over a period of at least 12 months. This approach reflects today's clinical practice, all the more as the prognostic value of PET imaging at mid-treatment or end-control is impaired by false-positive and false-negative results[6–8,17]. Furthermore, the low grade of the majority of NHL patients may have an impact on the results. Indeed, due to considerable necrosis even at diagnosis, VACT criteria may prove less efficient in aggressive lymphoma subtypes such as diffuse large B-cell lymphoma or Burkitt lymphoma even though rim enhancement due to persistent peripheral vascularization is likely. In these tumours, the additional use of more sensitive methods such as volume perfusion CT (VPCT) could enhance assessment of vascularity and tumour vessel permeability. Studies to address these issues are currently under way. The retrospective character of the analysis and the small number of non-responders are further limitations, which warrant prospective follow-up studies in order to validate our results.

The evaluation of VACT of residual masses during chemotherapy is certainly not a definite and infallible criterion for the estimation of disease activity. However, these data are collected in every standard CECT and may provide additional information about the disease status. Therefore, compared with volume measurements alone, our pilot data suggest that VACT may prove to be a valuable surrogate parameter. A good prognostic value in the response assessment, especially of aggressive lymphomas, has been reported for both FDG-PET/CT and gallium scintigraphy (^{67}Ga)[23,24]. Compared with PET/CT, VACT has less economic burden but fails to depict the metabolism in a straightforward manner. Characterization of additional qualities such as lymphoma perfusion and permeability (k-trans) via VPCT will give us new, functional parameters at hand and may aid in the risk stratification and treatment optimization[25,26]. Thus, VPCT in combination with VACT may be a true alternative to PET/CT in the response assessment of lymphomas. Further studies to elucidate this notion are needed.

Conclusion

According to our results, mid-treatment response assessment of residual masses in patients with HD and NHL using VACT yields high sensitivities and specificities and may aid in the CT evaluation as an additional surrogate parameter.

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