Therapy Response Evaluation of Malignant Lymphoma in a Multicenter Study: Comparison of Manual and Semiautomatic Measurements in CT

Zusammenfassung ▼
Ziel: Multizentrischer Vergleich von manuellen ein-/bi-dimensionalen Messungen und semi-automatischen ein-/bi-dimensionalen und volumetrischen Messungen zur Beurteilung des Therapieansprechens beim Malignen Lymphom in CT-Verlaufskontrollen.


Key words
- lymphoma
- staging
- abdomen
- mediastinum
- thorax
- computed tomography
und sollten daher insbesondere in klinischen Studien zukünftig aber auch in die klinische Routine implementiert werden.

Kernaussagen:
- Semi-automatisches Volumen und bi-dimensionaler WHO-Messungen reduzieren die Anzahl von Fehlklassifikationen beim Therapieansprechen signifikant (p < 0.05)
- Die manuelle Auswertung von Lymphknoten auf Basis uni-dimensionaler Parameter ist der semi-automatischen in einem Multicenter-Setting unterlegen
- Semi-automatische quantitative Softwaretools sollten zur Auswertung in klinischen Studien obligat eingesetzt und zukünftig auch in der klinischen Routine implementiert werden.

Introduction

Revised RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) as well as standardized Non-Hodgkin-Lymphoma (NHL) response criteria have underlined the importance of multidetector computed tomography (MDCT) as the primary lymph node imaging modality in clinical radiology practice [1–3]. Although firmly established in the setting of clinical trials, the need for systematic quantitative imaging in the daily routine is questioned to some extent by many radiologists [4]. However, with the worldwide introduction of comprehensive cancer centers, it has become much more apparent that many oncology patients are routinely included in clinical trials by tumor board decisions based – among other criteria – on quantitative imaging data. It is remarkable that 94% of oncologists at 55 U.S. cancer institutions expect oncology patients to undergo quantitative measurements regardless of enrollment in clinical trials [4,5]. Changes in tumor size are routinely assessed using manually acquired metrics such as long axis diameter (LAD) and short axis diameter (SAD) [1, 6–11]. Manual acquisition of these uni-dimensional parameters bears inherent sources of error as demonstrated by the high interobserver and intraobserver variability [12, 13] potentially leading to misinterpretations in tumor response assessment [14].

Previous studies have already demonstrated the technical feasibility of methods for semi-automated lymph node measurement in oncology, specifically addressing measurement precision and the necessity of correction [15–19]. Robust, user-friendly semi-automated tools in particular have shown greater reproducibility compared to their manual counterparts in the assessment of lymph nodes in various oncologic diseases [15, 16, 20].

In view of the increasing mobility of oncological patients between different medical centers, the influence of the reader (different readers in different institutions) becomes more apparent. Thereby, the prerequisites for a reproducible quantitative tumor burden assessment should lie between two extreme poles: a) variance of assessment allows only for a single-center assessment by one and the same radiologist over the whole course of the oncologic disease and b) the method of quantitative measurements is independent of the individual radiologist and institution. To the best of our knowledge, multi-center studies that comparatively define such prerequisites for a) a manual approach and b) a semi-automated tumor burden assessment are lacking. This multi-center study aims to determine the impact of manual and semi-automated lymph node measurements, measurement parameters (uni- versus multidimensional) and readers (different centers) on therapy response classification in the follow-up of patients with malignant lymphoma.

Material and Methods

Patients

63 consecutive patients (male/female 40 (64%)/23; 22–83 years, mean age of 56 ± 13 years) with histologically confirmed Hodgkin lymphoma (n = 10, 15.4%) and non-Hodgkin lymphoma (n = 53, 84.6%) including follicular lymphoma (15.4%), mantle-cell lymphoma (6.1%), marginal zone lymphoma (3.1%), other indolent B-cell lymphoma (47.7%) and T-cell lymphoma (12.4%), were included in this retrospective study. The criteria for inclusion were a) initial diagnosis of lymphoma (88%) or b) relapse of malignant lymphoma (12%). Patients already on chemotherapy prior to CT were excluded. All patients underwent a contrast-enhanced MDCT scan prior to therapy for staging and after two cycles of chemotherapy (mean time between baseline and final staging: 106 days; range 15–448 days). Written informed consent for MDCT was obtained from all patients before examination. The study was approved by the local ethics committee and conducted according to the guidelines of the institutional review board.

Data acquisition, preparation and transfer

Data acquisition

All examinations were performed at the main study center (study site 1) in order to minimize potential variations due to different scanner geometries and protocol parameters. The standardized CT examinations of the cervico-thoracic and abdominal region were performed using a 64 multislice CT scanner (Somatom Definition; Siemens Medical Solutions, Forchheim, Germany). The contrast agent (Ultravist 370®, Bayer Schering Pharma AG, Leverkusen, Germany) was applied with a constant injection rate of 3 ml/s. The scan delay was adapted to the anatomic regions (cervico-thoracic 45 s and abdominal 85 s). Images were obtained at 120 kV with a 32 × 0.6 mm² collimation, using a special dose-modulation template for radiation exposure reduction (CARE dose®) [21]. All CT data sets were reconstructed at a slice thickness of 1.5 mm with a reconstruction increment of 0.6 mm, which was revealed in a recent study as the optimal slice thickness for segmentation [15]. The scanning protocol did not differ from the standardized protocol used in the clinical routine.

Data preparation with labeling of target lymph nodes

At study site 1 CT data sets were transferred to a separate workstation (Oncology Prototype Software (Fraunhofer MEVIS, Sie-
For statistical analysis (see below) Weßling J et al. Therapy Response Evaluation node evaluation based on an extended version of the lung lesion This software includes an algorithm for semi-automated lymph radiologists at each site, separately and independently evaluated the digitally tagged lymph nodes. The data semi-automated lymph node segmentation was performed by the same blinded radiologists at each site, separately and independently in a randomized fashion in order to avoid memory bias (with regard to diameter level and orientation). Manual measurement encompassed digital caliper measurements of LAD (mm) and SAD (mm) on axial CT images of the reader’s choice (cine mode). Manual bi-dimensional WHO (mm²) was calculated as the product of manual LAD and SAD.

Semi-automatic evaluation
Semi-automatic lymph node segmentation was performed by the same blinded radiologists at each site, separately and independently in a randomized fashion, using dedicated segmentation software.

This software includes an algorithm for semi-automated lymph node evaluation based on an extended version of the lung lesion segmentation approach [13, 23 – 25]. The semi-automated segmentation process was started by drawing a stroke on the tagged lymph node of any particular slice. The volume of interest (VOI) and thresholds (histogram analysis within the VOI) for initial segmentation of the lymph node originating at the center of the stroke were estimated automatically. The initial segmentation results were displayed on the basis of region-growing-based algorithms, whereas ellipsoid approximation, distance map calculation and watershed algorithms separated adjacent structures of similar density such as blood vessels and muscle tissue. A 3D viewer, producing multiplanar reconstructions, delivered visual verification of the segmentation result. Dedicated correction tools could be used to modify any unsatisfactory segmentation results by drawing 2D contours on ill-segmented portions in any of the three 2D planes, followed by conversion into a 3D correction using an extrapolation process (Fig. 2). The following parameters were automatically displayed: LAD (mm), SAD (mm), volume (ml), and bi-dimensional WHO (mm²). Approved manual caliper and semi-automatic measurements at each site were transferred automatically into an Excel® table by dedicated software in order to prevent manual data transfer errors.

Time measurement
Time measurements taken with a stopwatch are subject to handling errors and limited assessment with a view to sub-processes. We therefore compiled a dedicated program for automatic time measurements without the need for interaction from the examining radiologist. During manual assessment, the time measurement was started when starting to scroll through the tagged lymph node (cine mode) and stopped on finalizing the LAD and SAD caliper measurements. The time for semi-automatic assessment was captured from the point of time at which a stroke was drawn on the tagged lymph node of any particular slice until correctness was verified. The correction time was recorded from activation of a correction tool until confirmation of correctness. An additional 4–6 s transfer time from the scanner to the workstation for manual and semi-automatic approach remained out of consideration.

Response assessment
Response criteria
To ensure the comparability of parameters in the same familiar units, measurements need to be converted and standardized as basically described by James et al. [26]. All volume and bi-dimensional measurements were therefore converted to diameters as recently published by different groups [16, 19, 27]. These effec-
The baseline and follow-up scans of each patient are shown on one screen in multiplanar reconstructions. The segmentation result of a malignant lymph node in the baseline and follow-up examination is displayed (yellow lines) a few seconds after starting segmentation. If the initial segmentation result is inadequate, corrections can be made using dedicated software tools. Once the segmentation result is confirmed as adequate and corrections have been made, a synopsis of the different segmentation parameters (e.g., volume) with changes in size under therapy is generated automatically.

Response classification
Response classification in this study was based on two different assumptions.

a) In order to avoid a selection and averaging bias and to examine the measurement quality and measurement precision of the different evaluation techniques, the "response classification per lymph node" was determined based on changes in the size of each single lymph node, irrespective of the patient concerned. As a restriction, this approach cannot be applied to clinically utilized classification systems.

b) The "response classification per patient" was based on target groups, i.e., in each patient the diameters of up to six target lymph nodes were summarized. The sum of each parameter was recorded at baseline and compared with the sum of the diameters at follow-up. Wrong classifications were assumed for sum diameter changes aberrant to the reference standard. This clinically applied classification system reduces measurement deviations by accepting averaging biases.

Statistical analysis
Statistical analyses were performed using SAS software, version 9.3 of the SAS system for Windows. Inferential statistics are intended to be exploratory (hypothesis generating), not confirmatory, and are interpreted accordingly. The comparison-wise type-I error rate is controlled instead of the experiment-wise error rate. The local significance level is set to 0.05. No adjustment
was made for multiple testing, hence an overall significance level was not determined and cannot be calculated.

Standard descriptive statistical analyses were performed for the target parameters of manual and semi-automatic LAD and SAD, semi-automatic bi-dimensional WHO and volume. Results are shown as mean values ± standard deviation. In order to compare semi-automatic and manual time parameters, the Student’s t-test for independent groups was applied to log-transformed time data. Time data are presented as median values [25 % quantile, 75 % quantile].

According to the relative change of lymph node sizes, a classification of response criteria was derived for each measurement parameter (see response criteria). The reference standard response was defined as the mean relative change across all parameters (i.e., reference = mean(relative change SAD manual, relative change SAD semi-automatic, relative change LAD manual, relative change LAD semi-automatic, relative change volume (as uni-dimensional equivalent diameters))). Each single parameter was compared to this reference standard with respect to the response classification. The classification results were described in terms of relative frequencies or odds ratios (95 % confidence limits).

Situation A (response classification per lymph node) entailed the process of fitting generalized linear mixed models. The dependent variable was the binary response classification (right/ wrong). The logit function was chosen as the link function with binomial distribution as the corresponding distribution. The measurement method was treated as a fixed effect. In order to account for multiple ratings of one lymph node, measurement correlations from each individual rater, and dependencies between lymph nodes in one patient, the parameters lymph node, reader and patient parameters were modeled as random effects with a compound symmetry covariance structure. To compare semiautomatic with manual measurement classification, a dummy variable was included as a fixed effect. The same was done to compare one-dimensional and multidimensional measurement classifications. To detect differences between anatomic regions, additional generalized linear mixed models were computed with the anatomic region of the lesion as a fixed effect. The influence of the study centers on classification results was also analyzed with the anatomic region of the lesion as a fixed effect. The same was done to compare semiautomatic with manual measurement classification, a dummy variable was included as a fixed effect. The same was done to compare one-dimensional and multidimensional measurement classifications. To detect differences between anatomic regions, additional generalized linear mixed models were computed with the anatomic region of the lesion as a fixed effect.

Table 1 provides a summary of the manual/semi-automatic measurement results. In total, 614 lymph nodes (307 baseline, 307 follow-up) were measured manually and semi-automatically in 63 patients (4.8 ± 3.3 lymph nodes/patient) at each site. The lymph nodes were evenly distributed in the thoracic (n = 129) and abdominal/pelvic (n = 125) region. Due to the relatively small anatomic volume, fewer lymph nodes were tagged in the cervical (n = 53) region.

**Table 1** Manual and semi-automatic lymph node analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>baseline</th>
<th>follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manual</strong> (all sites)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD [mm]</td>
<td>24.2 ± 9.9</td>
<td>17.5 ± 9.1</td>
</tr>
<tr>
<td>SAD [mm]</td>
<td>15.9 ± 7.3</td>
<td>10.9 ± 6.3</td>
</tr>
<tr>
<td>bi-dimensional WHO [mm]</td>
<td>22.0 ± 9.2</td>
<td>15.4 ± 8.2</td>
</tr>
<tr>
<td>semi-automatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD [mm]</td>
<td>24.4 ± 10.3</td>
<td>17.5 ± 9.4</td>
</tr>
<tr>
<td>SAD [mm]</td>
<td>15.9 ± 7.7</td>
<td>10.7 ± 6.7</td>
</tr>
<tr>
<td>bi-dimensional WHO [mm]</td>
<td>22.1 ± 9.8</td>
<td>15.3 ± 8.7</td>
</tr>
<tr>
<td>Volume [mm³]</td>
<td>20.5 ± 8.9</td>
<td>14.9 ± 8.0</td>
</tr>
</tbody>
</table>

Mean ± standard deviation (SD) of manual and semi-automatic long axis diameter (LAD, mm) and short axis diameter (SAD, mm) for baseline and follow-up examinations across all study sites. Bi-dimensional WHO and volume were given as unidimensional equivalent diameters in mm. Lymph nodes in the cervical, thoracic (axillary, mediastinal and hilar), abdominal (retroperitoneal, mesenteric), and pelvic (parailiac, inguinal) region were analyzed.

Overall site-specific therapy response classification was comparable between the manual uni-dimensional parameters (LAD 79.5 %/SAD 77.1 %) and the semi-automatic SAD (SAD 77.5 %). Statistical significance was observed for semi-automatic LAD (83.1 %) compared to manual LAD/SAD (p = 0.0007/p < 0.0001). Semi-automatically derived multidimensional parameters allowed for a significantly more accurate response to therapy classification than either the manual or the semi-automatic uni-dimensional parameters (e.g.,

**Results**

**Lymph node characteristics**

- **Table 1** summarizes the time expenditure. Manual lymph node measurements (LAD and SAD) took a median time of 12.1 s [9.5 s/17.9 s] on average across all sites and readers. Without any further need for correction (41.9 % of all cases), semi-automated segmentation (12.2 s; [9.3 s/16.0 s]) was equivalent to the manual approach at all study sites. The time required for semi-automated segmentation increased consecutively from 12.2 s [9.5 s/15.3 s] to 38.2 s [26.7 s/57.8 s] when correction tools were used (56.6 % of all cases). With regard to all lymph node segmentations (with and without the use of correction tools), the median time of 23.0 s [12.9 s/42.4 s] was significantly higher than with the manual approach (12.2 s, p < 0.001).

**Therapy response classification**

- **Table 2** details the numbers of correctly and incorrectly classified therapy response (A. per lymph node and B. per patient classification) across all centers. In addition, **Table 3, 4** outline the corresponding levels of significance for each of the different manual and semi-automatic parameters.

- **a) “Response classification per lymph node”**: Across all sites, the precision of the correct therapy response classification was comparable between the manual uni-dimensional parameters (LAD 79.5 %/SAD 77.1 %) and the semi-automatic SAD (SAD 77.5 %). Statistical significance was observed for semi-automatic LAD (83.1 %) compared to manual LAD/SAD (p = 0.0007/p < 0.0001). Semi-automatically derived multidimensional parameters allowed for a significantly more accurate response to therapy classification than either the manual or the semi-automatic uni-dimensional parameters (e.g.

**Time evaluation**

- **Fig. 3** summarizes the time expenditure. Manual lymph node measurements (LAD and SAD) took a median time of 12.1 s [9.5 s/17.9 s] on average across all sites and readers. Without any further need for correction (41.9 % of all cases), semi-automated segmentation (12.2 s; [9.3 s/16.0 s]) was equivalent to the manual approach at all study sites. The time required for semi-automated segmentation increased consecutively from 12.2 s [9.5 s/15.3 s] to 38.2 s [26.7 s/57.8 s] when correction tools were used (56.6 % of all cases). With regard to all lymph node segmentations (with and without the use of correction tools), the median time of 23.0 s [12.9 s/42.4 s] was significantly higher than with the manual approach (12.2 s, p < 0.001).
Korrektheit der Beurteilung des Therapieansprechens anhand Annahme A) "Response classification per lymph node" und B) "Response classification per patient". (A). Die Beurteilung war über alle Studienzentren (n = 614 Lymphknoten oder n = 126 Patienten) bestimmbar. Unter Annahme B wurde die Anzahl von Misklassifikationen um 9,6% bei Verwendung von semi-automatischen bi-dimensional WHO und dem Volumen im Vergleich zu manuellem LAD und SAD reduziert. 

**Table 2** Therapy response classification across all sites based on the two different assumptions (per lymph node/per patient) in this study.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>correct A</td>
<td>1942</td>
<td>1884</td>
<td>2123</td>
<td>2030</td>
<td>1893</td>
<td>2185</td>
</tr>
<tr>
<td>incorrect A</td>
<td>502</td>
<td>560</td>
<td>321</td>
<td>414</td>
<td>551</td>
<td>259</td>
</tr>
<tr>
<td>B correct</td>
<td>431</td>
<td>419</td>
<td>467</td>
<td>454</td>
<td>408</td>
<td>478</td>
</tr>
<tr>
<td>incorrect B</td>
<td>78</td>
<td>90</td>
<td>42</td>
<td>55</td>
<td>101</td>
<td>31</td>
</tr>
<tr>
<td>false worse A</td>
<td>50</td>
<td>33</td>
<td>18</td>
<td>34</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>false worse B</td>
<td>28</td>
<td>55</td>
<td>24</td>
<td>21</td>
<td>78</td>
<td>24</td>
</tr>
<tr>
<td>false worse C</td>
<td>21</td>
<td>9</td>
<td>18</td>
<td>34</td>
<td>22</td>
<td>7</td>
</tr>
</tbody>
</table>

Correctness of therapy response classification according to A) "Response classification per lymph node" and B) "Response classification per patient". (A). Response classification was summarized and calculated across all study sites (n = 614 lymph nodes or n = 126 patients). Assumption B revealed a mean reduction in wrongly classified patients of 9.6% for semi-automatic bi-dimensional WHO and volume compared to manual LAD and SAD.

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Table 3  
**Response classification per lymph node based on manual and semi-automatic measurements (A).**

<table>
<thead>
<tr>
<th>parameter</th>
<th>LAD manual</th>
<th>LAD semi-automatic</th>
<th>SAD manual</th>
<th>SAD semi-automatic</th>
<th>bi-dimensional WHO manual</th>
<th>bi-dimensional WHO semi-automatic</th>
<th>volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD manual</td>
<td>X</td>
<td>3.6</td>
<td>2.4</td>
<td>2.0</td>
<td>7.4</td>
<td>9.9</td>
<td>7.5</td>
</tr>
<tr>
<td>LAD semi-automatic</td>
<td>0.00007</td>
<td>X</td>
<td>6.0</td>
<td>5.6</td>
<td>3.8</td>
<td>6.3</td>
<td>3.9</td>
</tr>
<tr>
<td>SAD manual</td>
<td>0.0326</td>
<td>&lt;0.0001</td>
<td>X</td>
<td>0.4</td>
<td>9.8</td>
<td>12.3</td>
<td>9.9</td>
</tr>
<tr>
<td>SAD semi-automatic</td>
<td>0.0702</td>
<td>&lt;0.0001</td>
<td>0.7435</td>
<td>X</td>
<td>9.4</td>
<td>11.9</td>
<td>9.5</td>
</tr>
<tr>
<td>bi-dimensional WHO manual</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>X</td>
<td>2.5</td>
<td>0.1</td>
</tr>
<tr>
<td>bi-dimensional WHO semi-automatic</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>X&lt;0.0001</td>
<td>0.0045</td>
<td>X</td>
<td>2.4</td>
</tr>
<tr>
<td>volume</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0068</td>
<td>0.8946</td>
<td>X</td>
</tr>
</tbody>
</table>

Results of the generalized linear mixed model: dependent variable = binary response classification, fixed effect = measurement method, random effects = patient, rater. Repeated observations = lymph node (all compound symmetry covariance structure). Volumetry and semi-automatic bi-dimensional WHO revealed significantly fewer misclassifications compared to all unidimensional parameters (e.g. LAD, SAD), whether derived manually or semi-automatically. This was consistent across all sites. Additionally, the differences (modulus) between the relative numbers (%) of correct therapy evaluation are displayed in italics.

Table 4  
**Response classification per patient (B).**

<table>
<thead>
<tr>
<th>parameter</th>
<th>LAD manual</th>
<th>LAD semi-automatic</th>
<th>SAD manual</th>
<th>SAD semi-automatic</th>
<th>bi-dimensional WHO manual</th>
<th>bi-dimensional WHO semi-automatic</th>
<th>volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD manual</td>
<td>X</td>
<td>4.5</td>
<td>2.4</td>
<td>4.5</td>
<td>9.2</td>
<td>7.1</td>
<td>7.6</td>
</tr>
<tr>
<td>LAD semi-automatic</td>
<td>0.041</td>
<td>X</td>
<td>6.9</td>
<td>9.0</td>
<td>4.7</td>
<td>2.6</td>
<td>3.1</td>
</tr>
<tr>
<td>SAD manual</td>
<td>0.477</td>
<td>0.018</td>
<td>X</td>
<td>4.5</td>
<td>11.6</td>
<td>9.5</td>
<td>10.0</td>
</tr>
<tr>
<td>SAD semi-automatic</td>
<td>0.278</td>
<td>0.018</td>
<td>0.496</td>
<td>X</td>
<td>13.7</td>
<td>11.6</td>
<td>12.1</td>
</tr>
<tr>
<td>bi-dimensional WHO semi-automatic</td>
<td>0.003</td>
<td>0.018</td>
<td>&lt;0.001</td>
<td>&lt;0.0001</td>
<td>X</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>bi-dimensional WHO manual</td>
<td>0.001</td>
<td>0.152</td>
<td>&lt;0.001</td>
<td>0.003</td>
<td>0.300</td>
<td>X</td>
<td>0.5</td>
</tr>
<tr>
<td>volume</td>
<td>0.012</td>
<td>0.170</td>
<td>0.003</td>
<td>0.002</td>
<td>0.453</td>
<td>0.811</td>
<td>X</td>
</tr>
</tbody>
</table>

Results of the McNemar’s test for clustered data adjusted for multiple ratings. Volumetry and semi-automatic bi-dimensional WHO revealed significantly fewer misclassifications compared to most unidimensional parameters (e.g. manual LAD, SAD) across all sites. No significant differences were found between semi-automatic bi-dimensional WHO and volume. Additionally, the differences (modulus) between the relative numbers (%) of correct therapy evaluation are displayed in italics.

**Per study site**  
Fig. 6, 7 illustrate the percentage of correct therapy response classifications per study site, as well as for each manual and semi-automatic parameter. Irrespective of the evaluation assumption (response classification per lymph node or per patient), the fraction of correctly classified therapy responses was found to be consistently and significantly higher for multi-dimensional parameters (e.g. manual or semi-automatic bi-dimensional WHO and volume) as compared to uni-dimensional parameters obtained either manually or semi-automatically.

**Influence of the measurement approach (manual versus semi-automatic) on correct lesion classification**  
The precision of the therapy response classification was significantly affected by the measurement approach, whether manual or semi-automatic. However, with an odds ratio of 1.18 times...
tion and measurement tools have demonstrated their technical time [31]. In the past decade, semi-automatic tumor segmenta-

especially by reducing variability across devices, patients and

courages further multidisciplinary research into the enhance-

marker Alliance of the Radiological Society of North America en-

[12, 16, 18, 25, 29]. Consequently, the Quantitative Imaging Bio-

metrics in CT imply a degree of precision which has to be viewed cri-

In oncological decision processes manually obtained tumor me-

ments have been undertaken. Fabel et al. [18] did not find any

ferences in response classification when using semi-automatic

response classification in this study was based, furthermore, on two different assumptions, namely

the presence of a lymph node and a clinical patient-based classi-

cation. In line with this and the IWC guidelines, the diameters of

up to six target lymphoma lesions were summarized and com-

pared between baseline and follow-up [2, 22]. This differentia-

tion was essential for unmasking the selection and averaging bia-

ses of clinically applied classification systems based on target
groups with sum diameters.

Only rudimentary investigations into the effects of interobserver

variability on tumor response classification in follow-up exami-

nations have been undertaken. Fabel et al. [18] did not find any

ifferences in response classification when using semi-automatic

measurements in melanoma patients, but admitted to con-

straints in the selected classification limits. In another recently

published single-center study of semi-automatic lymph node

segmentation, semi-automatic volumetry and bi-dimensional

WHO permitted classifications that were significantly more ac-

urate than those based on manual one-dimensional parameters

[29]. According to this study, one of the main findings is that, on a

"per lymph node" as well as on a "per patient" basis, multidimen-

sional parameters – whether obtained manually or semi-auto-

matically – allowed for a significantly more accurate therapy re-

response classification than uni-dimensional parameters (e.g.

volume 87.0 % vs. manual SAD 79.5 %, p < 0.001). In this study,

these findings were confirmed for all study centers, irrespective

of the anatomic region. The inferior performance of the one-di-

mensional parameters SAD and LAD in our study is therefore an

argument against proposals to promote uni-dimensional metrics

in follow-up assessments of malignant lymphomas [22].

On the patient level, semi-automatic “volumetry” and “bi-dimen-

sional WHO” significantly reduced the number of wrongly classi-

fied lymphoma patients consistently across all study sites by ap-

proximately 9.6 % (7.9 – 13.5 %), thus confirming the results of an

to their use in the clinical routine. To the best of our knowledge, it

is not yet clear whether semi-automatic software tools and the

derived uni- and multidimensional parameters (volumetry) har-

bor such potential with respect to assessing therapeutic re-

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(95 % CI 1.08 – 1.29, p = 0.0003) the probability of correct classifi-

cation was significantly higher using the semi-automatic instead

of the manual approach.

Center-specific influence on correct patient classification

As revealed by the generalized linear mixed model analyses, the

study center has a significant influence on therapy response clas-

sification, irrespective of the chosen approach (manual or semi-

automatic). Compared to the manual approach, however, the in-

fluence of the study center on correct therapy classification is sig-

ificantly less relevant when semi-automatic methods are used.

Discussion

In oncological decision processes manually obtained tumor met-
rics in CT imply a degree of precision which has to be viewed cri-
tically in terms of measurement variability and reproducibility
[12, 16, 18, 25, 29]. Consequently, the Quantitative Imaging Bio-

marker Alliance of the Radiological Society of North America en-
courages further multidisciplinary research into the enhance-

ment of the value and practicality of quantitative imaging,
especially by reducing variability across devices, patients and
time [31]. In the past decade, semi-automatic tumor segmenta-
tion and measurement tools have demonstrated their technical
feasibility with regard to lung nodule and liver lesion segmenta-
tion [13, 20, 32 – 34]. Recent studies specifically addressed the
aspects of reproducibility and variability between different readers
in the semi-automated segmentation of tumor-affected lymph
nodes, and found inter-user differences to be reduced by a factor
of approximately 1.4 to 3.0 compared to the manual approach
[16, 19, 35].

These feasibility studies are limited by their lack of data on fol-

low-up examinations, whereby inter-user differences could be

aggravated, e.g. due to variable lymph node orientation caused
by shrinkage. In view of the increasing mobility of oncological pa-
tients, the influence of the reader (different readers in different
institutions) on the assessment of follow-up examinations and
therapy response classification is becoming more apparent. The
ideal quantitative measurement tool should naturally provide
highly reproducible measurements that are more or less unin-
fluenced by the attending radiologist and institution, do not de-

mand an excessive amount of time and are robust when it comes

Fig. 4 Size regression of lymph node under therapy and segmentation. Segmentation results on baseline (BL) and follow-up (FU) scans of a sample inguinal lymph node under therapy at the five study sites (1 – 5). The yellow contour lines indicate adequate segmentation results that largely corres-
dpond between the five study sites.

Abb. 4 Größenabnahme eines segmentierten Lymphknotens unter The-

rapi e. Segmentierungsergebnisse in der Baseline (BL)- und der Follow-up-

(FU)-Untersuchung unter Therapie in den fünf Studienzentren (1 – 5). Die
gelben Konturlinien verdeutlichen die Segmentierungsergebnisse, die zwis-
chen den Studienzentren eine große Übereinstimmung aufweisen.
earlier single-center study [29] on semi-automatic lymph node segmentation, which transferred lower measurement variability into a reduction of wrongly classified lymphoma patients of 10%. There is a further implication from our data, namely that manual bi-dimensional WHO was comparable to its semi-automatic counterpart and semi-automatic volumetry on a patient level. This finding was consistently observed at all study sites. Consequently, the relevance of using semi-automatic software tools, especially in clinical trials, has to be questioned. On a per lymph node level, however, the precision of manual WHO (86.9%) was found to be significantly inferior to semi-automatic WHO (89.4%, p = 0.0045) and semi-automatic volumetry (87.0%, p = 0.0068).

Indeed, a number of patients have only a limited number of target lesions, e.g. two or three, and the radiological approach (manual vs. semi-automatic) becomes a significant factor in correct response classification. Therefore, it seems reasonable to use semi-automatic multidimensional parameters in a clinical or study setting, while we do not see any advantages for semi-automatic volumetry over semi-automatic bi-dimensional WHO. Our results furthermore indicate that the correctness of therapy response classification across all study centers is significantly affected by both measurement approaches (manual or semi-automatic). The odds ratios showed a 1.18 times (95 CI: 1.08 – 1.29) higher probability of correct patient classification (p = 0.0003).
using the semi-automatic instead of manual approach. As revealed by the generalized linear mixed model analyses, we found the study center to have a significant influence on the therapy response classification and also found the semi-automatic quantitative measurement tools to be dependent on the radiologist and institution concerned. However, compared to the manual approach, the influence of the study center on therapy classification is significantly less relevant when using the semi-automatic method. Semi-automatic quantitative software tools may therefore help to significantly reduce wrong classifications that arise from manual assessment and the examining institution, thus favoring semi-automatic therapy evaluation, especially in a study environment.

Time expenditure – among other criteria – has a decisive influence on the acceptance and dissemination of segmentation software tools in oncology. In line with a recent study [29], semi-automatic lymph node segmentation in our investigations allowed for true-to-detail lymph node segmentation across all study sites at the first attempt in 43.4% of lymph nodes with a comparable time expenditure as compared to the manual approach (12.1 s manually vs. 12.2 s semi-automatically). The evaluation time for all segmentations at all study sites using the semi-automatic software tool was almost twice that of manual evaluation (12.1 s manually vs. 23.0 s semi-automatically). The increased time expenditure for the semi-automatic approach is highly consistent with the results published by Fabel et al. (mean 37s; range 20–70 s [35]), but has to be put into perspective: Uni-dimensional and multi-dimensional measurements are automatically displayed without the need for further manual interaction and are automatically transferrable into oncologic reporting systems in

**Fig. 6** Therapy response evaluation per lymph node with regard to study site. Relative rates of correct therapy response evaluation per lymph node with regard to study sites. Across all the study sites, the correctness of the therapy response evaluation was lower for manual and semi-automatic LAD and SAD, while the rate for bi-dimensional WHO and volume was higher. (Abb. 6 Beurteilung des Therapieansprechens pro Lymphknoten unter Berücksichtigung des Studienzentrums. Relative Raten korrekter Beurteilung des Therapieansprechens pro Lymphknoten unter Berücksichtigung des Studienzentrums. Über alle Studienzentren war der Anteil korrekter Beurteilungen des Therapieansprechens geringer für den manuellen und semi-automatischen LAD und SAD während diese für den bi-dimensionalen WHO und das Volumen höher war.)

**Fig. 7** Therapy response evaluation per patient with regard to study site. Relative rates of correct therapy response evaluation per patient with regard to study sites. Across all the study sites, the correctness of therapy response evaluation was significantly lower for manual and semi-automatic LAD and SAD, while the rate for bi-dimensional WHO and volume was higher. (Abb. 7 Beurteilung des Therapieansprechens pro Patienten unter Berücksichtigung des Studienzentrums. Relative Raten korrekter Beurteilung des Therapieansprechens pro Patienten unter Berücksichtigung des Studienzentrums. Über alle Studienzentren war der Anteil korrekter Beurteilungen des Therapieansprechens geringer für den manuellen und semi-automatischen LAD und SAD während diese für den bi-dimensionalen WHO und das Volumen höher waren.)
an RIS/PACS environment. In the manual approach, the docu-
mentation and calculation of manual WHO – which was not in-
cluded in the time measurements of this study – have to be per-
formed by the attending radiologist and are likely to increase the
total operation time as well as cause transfer biases through
manual interactions.

This study is limited to the extent that it does not allow compar-
ison with an exact reference standard, as is the case with a phan-
tom study. We used the manually and semi-automatically ob-
tained metric parameter as an internal reference standard,
which is accepted in the literature for the analysis of segmenta-
tion results, e.g. in pulmonary nodules and lymph nodes [13,
16]. The transferability of these results from lymphoma patients
to other malignant diseases seems reasonable but must be sup-
ported by additional studies. Furthermore, correlation analysis
to therapy response evaluation based on semi-automatic lymph
node measurements and therapy outcome was not covered by
this study and should be included in a future analysis. This study
also departs from previous studies by being the first to provide
data on multi-observer/multicenter variability and the influence
on therapy response classification.

In summary this multicenter study revealed semi-automatic seg-
mentation to be robust and time efficient, with acceptable time
expenditure compared to conventional manual lymph node as-
sessment. With regard to therapy response classification, semi-
automated multidimensional parameters (“volumetry” and “bi-
dimensional WHO”) significantly reduce the number of wrongly
classified lymphoma patients across all study sites by approxi-
amately 9.6% (interval across all study sites: 7.9 – 13.5%, p < 0.05)
and permit a significantly more accurate therapy response clas-
sification than uni-dimensional parameters. Semi-automatic
quantitative software tools may help to significantly reduce
wrong classifications that arise from manual assessment meth-
ods and differences between the examining institutions. In con-
clusion, semi-automatic quantitative software tools should be
implemented in clinical studies and desirably in the clinical rou-
tine.

Affiliations
1 Dept. of Clinical Radiology, University of Muenster, Germany
2 Dept. of Medical Informatics and Biomathematics, University of Muenster, Germany
3 Dept. of Oncology, University of Muenster, Germany
4 Dept. of Clinical Radiology, University of Munich, Germany
5 Clinic for Diagnostic Radiology, University Hospital Schleswig-Holstein
Campus Kiel, Germany
6 Department for Diagnostic and Interventional Radiology, University of
Mainz, Germany
7 Dept. of Diagnostic Radiology, University of Marburg, Germany
MEVIS, Fraunhofer, Bremen, Germany

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