# VOLUMETRIC CHANGES BASED ON COMPUTER TOMOGRAPHY AFTER THE FIRST TREATMENT OF LYMPHOMA PATIENTS

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**Abstract: The purpose of this study was to volumetrically evaluate the treatment outcome of non-Hodgkin's lymphoma (NHL) patients and to test the ability of the semiautomatic segmentation program Anatomatic™ to analyse computer tomography (CT) -data. There were 20 patients (aged 34 – 75 years) who underwent scanning procedures before and after the first chemotherapy treatment. The cases included 17 abdominal bulky tumours and three from the thorax region. The mean tumour volume before the first treatment was 850 cm$^3$ (110 – 4 500 cm$^3$) and after the treatment 540 cm$^3$ (62 – 2 800 cm$^3$). The average volume decline was 38.1 %. However, the volume decline of only four patients was big enough to be classified as partial response. Intraobserver variation was 5.7 % (0.2 – 13.6 %) and interobserver variation 11.2 % (0.5 – 32.9 %). The software proved to be applicable to experienced radiologists, when the original films are available for detail checking and the clinical/radiological examinations are optimally performed.**

## Introduction

Volumetric studies consider the shape of the tumour and thus provide a more accurate estimation of the whole tumour burden than uni- or two-dimensional measurements [1 - 3]. It has even been constituted that in some cases the prognosis of the patients can change when 3D based analysis is used [2]. However, there are also controversial results, depending on the shape of the mass [4]. On the other hand, for reasons not yet fully understood, the number of non-Hodgkin's lymphoma patients is increasing [26]. This study evaluates the ability of the CT based volumetric analysis to contribute the prognostics of non-Hodgkin lymphomas.

Anatomatic™ is a semiautomatic segmentation program and it has given promising results with magnetic resonance imaging (MRI) [5-8]. Only few studies have been reported from the CT field [9]. This study is the first that uses Anatomatic™ software in analysing CT-data at this scale. Also suitability of the software is discussed. This study is a part of a more comprehensive research project, which comprises evaluation of the treatment outcome of the whole treatment process using MRI, CT and positron emission tomography (PET) based volumetry.

## Materials and Methods

The material of this study consisted of 22 NHL patients who met the selection criteria from February 2002 to August 2004 at the Department of Oncology in Tampere University Hospital in Finland. The following criteria were considered: age 16-78 years, a histologically confirmed non-Hodgkin's lymphoma needing chemotherapy and the minimum diameter of the biggest tumour bulk 3 cm. In addition, patient's performance status had to be better than Zubrod [10] class 4. Gravidity, psychosis, diabetes with insuline treatment, HIV-positivity, AIDS or other serious disease preventing chemotherapy or another malignity were exclusion criteria.

Two patients were excluded from this analysis; the 10$^{th}$ patient passed away before scanning processes had been fully performed and the 21$^{st}$ patient found the project procedures too hard to manage and choose to drop out as well. The final 20 patients involved six women and 14 men whose average age was 62.3 years, (range 34.8 - 75.8 years), at the time of the first CT examination. There were 17 abdominal tumour masses and three from the thorax region. Low-grade NHL was diagnosed for 12 patients and high/medium high grade for eight. Of the 20 patients, 12 had a primary case. In addition to cytostatics, 11 of the patients got anti-CD20 antibody treatment (rituximab) (Table 1).

The native and enhanced helical-CT scans were done with Somaton +4 (Siemens, Erlangen, Germany) before and within a week after the first treatment. The volumes were analysed from data with slice thickness of 3 mm. Both intravenous and oral contrast medium was used.


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The cut-off points of the ROI (region of interest) were determined based on the anatomic structures which limit the most of the tumour burden and which can easily be localized in both scan sets (Table 1).

For thorax bulks, carina and os hyoideum limited the tumour burden and for abdominal masses the kidney level was taken into consideration, except the patient number 4 and 16. With the fourth patient, pubis symphysis and presacral vertebra limited the ROI area and with the patient 16 the spleen level was taken into consideration. The cut-off points and the lining of the tumour masses were carefully determined from the original films with a cooperation of an intern and a radiologist. About 40 slices usually covered the ROI.

The tumour burden was defined from the digitally processed enhanced axial scans. The CT scans were analysed with a standard PC in Windows environment on a double screen with a resolution of 3200x1200 pixels. The volumetry was done with the semiautomatic segmentation program Anatomatic™ applying the IARD-algorithm [11]. Segmentation and volumetry procedure required manual window setting, which was done subjectively by the observer. In addition, according to the tissue intensities, the desired scale could be segmented selecting appropriate threshold coefficients. Segmentation option was used as much as possible and tumour margins were finished manually with the help of the original CT-films. The tumour area was defined from each slice at the ROI with the region growing tool which searches the same intensities inside the desired area. The second version of the software was used, because it was more insensitive to breakdown when image files were processed. Otherwise it followed the same principles as the first version [11]. The software displayed voxels from which the final volume of the tumour burden was calculated with the multiply factor (mf) (1).

$$mf = \frac{fov^2}{matrixsize^2} \cdot slicethickness = \frac{500^2}{512^2} \cdot 3mm^3 \quad (1)$$

fov=field of view

The volume change was determined with simple per cent calculations (2).

$$change = \frac{V(before) - V(after)}{V(before)} \cdot 100\ \% \quad (2)$$

The software had been calibrated earlier using phantoms with an error of only 1.5 % [11]. To test the reproducibility and accuracy, inter- and intraobserver studies were performed over 8 weeks after the initial observations. For this, six patients were selected randomly. The pre-treatment scan sets of the patients 2, 8, 9, 14, 16 and 18 were reanalysed using the same methods as described earlier. In the interobserver analysis, an intern colleague analysed the scans with a radiologist. The variation was determined applying the same simple per cent calculations as described earlier (2).

Table 1: Patient and disease characteristics

| Patient no. | Age (years) | Sex | ROI | Grade | Status | Treatment |
|---|---|---|---|---|---|---|
| 1 | 67 | F | Thorax | high/med.high | Relapsed | Cytostatics |
| 2 | 61 | F | Abdomen | high/med.high | Primary | Cytostatics |
| 3 | 75 | F | Abdomen | low | Primary | Cytostatics |
| 4 | 74 | M | Abdomen | low | Relapsed | Cytostatics |
| 5 | 62 | M | Abdomen | low | Relapsed | Cytostatics+antibody |
| 6 | 72 | F | Abdomen | low | Relapsed | **C**ytostatics |
| 7 | 63 | M | Abdomen | low | Relapsed | Cytostatics |
| 8 | 71 | M | Abdomen | high/med.high | Primary | Cytostatics |
| 9 | 56 | M | Abdomen | high/med.high | Primary | Cytostatics+antibody |
| 11 | 72 | M | Abdomen | low | Primary | Cytostatics+antibody |
| 12 | 48 | F | Abdomen | low | Primary | Cytostatics+antibody |
| 13 | 75 | M | Abdomen | high/med.high | Relapsed | Cytostatics |
| 14 | 63 | F | Abdomen | high/med.high | Primary | Cytostatics+antibody |
| 15 | 53 | M | Abdomen | high/med.high | Primary | Cytostatics+antibody |
| 16 | 56 | M | Abdomen | high/med.high | Primary | Cytostatics |
| 17 | 49 | M | Thorax | low | Primary | Cytostatics+antibody |
| 18 | 34 | M | Abdomen | low | Primary | Cytostatics+antibody |
| 19 | 56 | M | Abdomen | low | Relapsed | Cytostatics+antibody |
| 20 | 66 | M | Thorax | low | Relapsed | Cytostatics+antibody |
| 22 | 74 | M | Abdomen | low | Primary | Cytostatics+antibody |


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## Results

Before the treatment, the average volume of the tumour masses at the ROI was 850 $cm^3$, (range 110 – 4 500 $cm^3$). After the treatment the average volume was 540 $cm^3$, (range 62 - 2 800 $cm^3$). Almost every patient's tumour burden had decreased after the first treatment. The average decline of the tumour volume was 38.1 %, (range -2.4 - 74.6 %). Only one patient had a tumour burden, which the treatment had not reduced, resulting in an increase of 2.4 % (Table 2.). However, according to the Recist response criteria [23] this was a stable disease.

The low-grade NHLs decreased 26.4 % and in the group of the high or medium high-grade NHLs the decline was 54.1 %. There was practically no difference between the primary and relapsed NHL groups, the average changes being 39.0 % and 36.7 %.

In the intraobserver studies, a reasonable average variation of 5.7 % (range 0.2 - 13.6 %) was revealed. In the interobserver studies the average variation was 11.2 %, (range 0.5 - 32.9 %). The variation was least with the patient 14. The most challenging case seemed to be the patient 9, demonstrating that the smaller the tumour burden, the more prone it was to misinterpretation (Table 3).

Table 2: Tumour volumes (*high/med. high-grade, no asterisk=low grade)

| Patient no. | V/$cm^3$ before | V/$cm^3$ after | Decrease/% |
|---|---|---|---|
| 1* | 1307.0 | 398.1 | 69.5 |
| 2* | 346.4 | 87.9 | 74.6 |
| 3 | 109.0 | 80.0 | 26.6 |
| 4 | 332.2 | 138.6 | 58.3 |
| 5 | 1178.9 | 795.7 | 32.5 |
| 6 | 1169.8 | 666.9 | 43.0 |
| 7 | 964.9 | 747.0 | 22.6 |
| 8* | 277.1 | 209.0 | 24.6 |
| 9* | 141.2 | 87.6 | 37.9 |
| 11 | 767.0 | 605.3 | 21.1 |
| 12 | 880.4 | 901.3 | -2.4 |
| 13* | 4480.3 | 2847.3 | 36.5 |
| 14* | 124.0 | 61.7 | 50.3 |
| 15* | 285.4 | 97.9 | 65.7 |
| 16* | 483.0 | 128.9 | 73.3 |
| 17 | 1031.4 | 481.9 | 53.3 |
| 18 | 1007.8 | 707.7 | 29.8 |
| 19 | 866.4 | 797.6 | 7.9 |
| 20 | 996.6 | 765.3 | 23.2 |
| 22 | 326.1 | 282.5 | 13.4 |
| average | 853.7 | 544.4 | 38.1 |

Table 3: Inter- and intraobserver variation

| Patient no. | Initial estimation | Intraobserver | | Interobserver | |
|---|---|---|---|---|---|
| | volume cm3 | volume cm3 | variation % | volume cm3 | variation % |
| 2 | 346.4 | 325.2 | 6.1 | 316.3 | 8.7 |
| 8 | 277.1 | 305.4 | 10.2 | 306.1 | 10.5 |
| 9 | 141.2 | 122.1 | 13.6 | 187.6 | 32.9 |
| 14 | 124.0 | 126.0 | 1.6 | 124.6 | 0.5 |
| 16 | 483.0 | 471.9 | 2.3 | 523.5 | 8.4 |
| 18 | 1007.8 | 1006.1 | 0.2 | 1069.5 | 6.1 |
| average | 396.6 | 392.8 | 5.7 | 421.3 | 11.2 |

## Discussion

The advantage of volumetric studies is based on the defining of tumour linings, which contribute the tracing of the 3D- structure of irregular masses [4, 12]. Due to capsules or other apparent contour representants, the volume determining of different organs or phantoms has been successful [12-14]. However, the tumour contours are not always obvious in vivo and to smoothen the margins defining intravenous and oral contrast medium are recommended [15-16]. In addition, scan quality, slice thickness, software and observer variation influence the accuracy of the results. Imaging can be also affected by peristalsis, respiration [16] and the position of the patient.

The previous study with Anatomatic and CT comprehended nasal airway assessment [9]. One of the goals of this study was to test to the ability of the software to analyse soft tissue lesions. The tumour masses of this study were mostly scattered and consisted of masses of different size. Van Hoe et al. [13] reported that the window setting influenced especially detection of small objects and this was confirmed also in this study. The intensities of small objects might have been different from the main bulk and thus require more careful threshold coefficient setting. In our study the intra- and interobserver variation were biggest with the patient 9, demonstrating the vulnerability of the detection of smaller masses.


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Schwartz et al. [18] reported that peritoneal lymph nodes were more difficult to distinguish than the lung tumours, because of the surrounding tissues. Also Helmberger et al. [16] reported that CT volumetry acquires good contrast qualities. Unfortunately, the contrast medium boluses had not spread evenly in every patient in this study, causing difficulties in the volumetric studies with Anatomatic™. Especially difficult was to define lesion margins at para-aortal abdominal sites, owing to complex structures including veins, fat, muscle and infiltrative tumour tissue (Figure 1, patient 6). However, the possibility to check details from original films helped the work done with Anatomatic™.

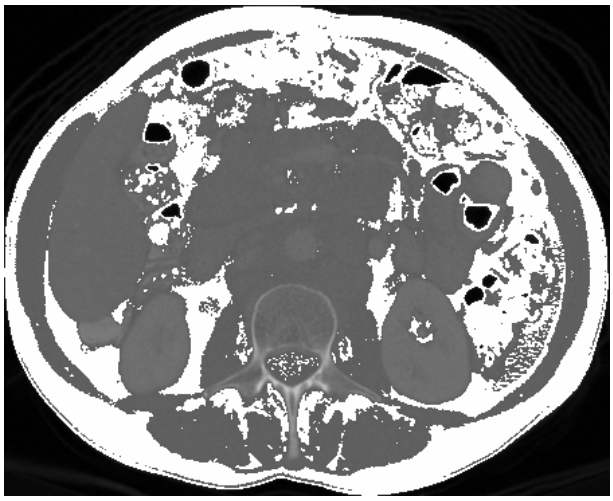

Figure 1. Problems of the kidney level: complex anatomy, peristalsis and poor intensity differences

Owing to the poor intensity differences, the soft tissue linings had to be drawn partly manually with the help of the original films, leading to an increased risk of misinterpretation. However, each slide was estimated carefully and in co-operation with a radiologist. Moreover, the use of helical CT and thin contiguous slices declined the partial volume effect and resulted in a more accurate estimation of the lesion. The scanning itself had been done according to the plans with high quality.

Nawaratne et al. [17] stated in 1997 that despite accidentally breathing, the estimation of kidney volume from helical CT data is accurate. Thus we believe that the respiration movement was negligible, taken kidney level and thorax measurements into consideration. More interesting was to observe the declining of the tumour burden, which might have affected the ROI in the abdominal site, when normal structures gained more space for themselves.

Observer variation depends on the edge recognition, the shape and the location of the site measured [22]. In addition, observer's segmentation skills develop in the course of experience, which can affect the accuracy. Both intra- and interobserver studies have been performed in a previous MRI study and the results showed a deviation, ranging from 3 % to 7 % [21]. In this study the intraobserver variation was 5.7 %, ranging from 0.2 to 13.6 %. Considering the more complex structures in this study and the fact that a variation of 15.3 % has been reported [27] for small, less-clearly demarcated structures, the result is reasonable for CT scans. Interobserver results showed a poorer overall variation of 11.2 %. On the other hand, measuring of the true volumes was not possible, so the true accuracy stays unrelieved.

Volumetry done with CT slices has been acknowledged to be quite time consuming when contours are not obvious [2]. The time consumption with Anatomatic™ has been quite reasonable in previous studies, ranging 15 – 20 min per patient with MRI and 30 – 50 min per patient with CT to 50 [5,11]. However, the time consumption is very case dependent. In this study, the easiest bulk masses were checked within half an hour, but widely spread abdominal masses took almost two hours to be determined.

In addition to tumour tissue, the lesion seen in CT scans is composed of necrosis, oedema, internal haemorrhage, calcification, fibrosis etc**.** Indistinct changes can be already seen in the surrounding tissues. Thus the pathologic status of a tumour and its surroundings is a more complex task to solve [18-20, 25]. Rodrigues [28] et al. demonstrated in 1999 that inhomogeneity in CT images was associated with a high-grade non-Hodgkin's lymphomas. The assessment of this was beyond the scope of this study. The average decline of the tumour volume was, however, bigger with patients with a high-/med. high-grade malignity. In addition, there were more intensity differences in the second scan set in this study, demonstrating that the treatment had affected the tumour morphology, although the volume had not decreased everywhere at the ROI. Naturally, further research and longer follow up of the patients are needed.

Due to a small sample size, the results of this study give a limited view on the volumetry of non-Hodgkin's lymphomas. The tumour volumes varied a lot, but obvious changes can be seen after the treatment, resulting in an average decline of volume of 38.1 %. According to Duffaud F. et al. [23] a decrease of 65 % in volume corresponds to partial response and a change between that and an increase of 40 % in volume is categorized as a stable disease. Four of the patients exceeded the partial response limit and others' tumour burden stayed stable, according to this guideline. However, these limits assume that the change is uniform and the tumour bulks are spherical, which are gross estimations. In addition, this study focused at the ROI, so the overall outcome of the patients who had a widely spread disease stays unaccomplished.


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## Conclusion

Kurek et al. [24] demonstrated that most importantly the initial tumour volume predicts the survival, in addition to the volume change after the treatment. This encourages to continue volumetric studies with Anatomatic™. This study revealed that CT based volumetric analyses done with Anatomatic™ are applicable to experienced radiologists, when the original films are available for detail checking and the clinical/radiological examinations are optimally performed.

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