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Evaluation of soft-tissue match methods for utilization in CBCT guided adaptive radiotherapy of lung cancer patients – clinical benefits, limitations and margin determination

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Supervision

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A summary of this work in Swedish

Mjukvävnad matchning för en noggrannare lokalisering av tumören under strålterapin

Bildstyrd strålterapi är en process bestående av att ta 2D eller 3D bilder under strålbehandlingens gång och används för att försäkra sig om att patienten är positionerad på samma sätt som referensbilden för att få samma ordinerade dos (beräknat på referens bilden). I det här arbetet har en 3D scanning av patientens positionering jämförts med en CT referensbild för patienten. Efter matchningen, som utförs precis innan varje behandling, korrigeras avvikelsen mellan bilderna. Avvikelserna i ryggraden (benmatch) eller i tumören (targetmatch) korrigeras genom att automatiskt flytta patienten på plats genom att flytta britsen i alla nödvändiga riktningar. 3D scanningen ger information om mjukvävnad och tumörens position. Lungtumören rör sig som följd av andningen och andra organens rörelse därför är matchningen på tumören att föredra istället för att matcha på ryggraden. För en säkrare och noggrannare matchning används därför 3D scanningen för lungcancer patienter. Det har gjorts en jämförelse mellan att matcha på tumören med en marginal runt om och att matcha på ryggraden.

Veckovisa 3D scanningar har använts för denna studie och matchningarna har utförts retrospektivt. Tumörens uppställningsavvikelse beräknades för både benmatch och targetmatch. Baserat på de avvikelserna har marginalen som behövs runt tumören beräknats. Marginalens uppgift är att försäkra sig om att tumören kommer att få den planerade dosen. Anatomiska förändringar och deras uppkomsttid har observerats under behandlingstiden.

Resultaten visade att targetmatch med en lite större marginal är stabilare att använda jämfört med targetmatch med mindre marginaler. Resultaten visade också att det behövs en mindre marginal runt tumören när matchningen har gjorts på tumören jämförts med matchningen på ryggraden. Mindre marginal innebär att man sparar friskvävnad ifrån onödig strålning. Observeringen av anatomiska förändringar visade att förändringarna skedde slumpmässigt och sammanfallen lungblåsa (då en del av lungan inte har fyllts med luft när man andas in) var den dominerande förändringen. Dagliga 3D scanningar skulle förebygga miss av anatomiska förändringar av betydelse.

Handledare: Patrik Sibolt, Wiviann Ottosson, Claus F. Behrens och David Sjöström.
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Abstract

Purpose*:* The aim of this study is to a) study the benefits and limitations with soft-tissue match for lung cancer patients, b) evaluate five different soft-tissue match methods, c) compare soft-tissue with bony match, d) find the stable surrogates to match on for obscured malignant lymph nodes, e) calculate CTV to PTV and OAR margins and volume of PTV for the corresponding margins, and f) study the anatomical changes associated with radiotherapy for lung cancer.

Material and methods*:* 23 lung cancer patients (16 NSCLC, 7 SCLC) treated with radiotherapy, with 135 weekly CBCT set-up images were retrospectively matched to the planning CTs by five different match methods using the registration software Offline Review, version 10.0 (Varian Medical Systems). Four match methods utilized the volume of interest (VOI) of the CT defined GTV, including the internal motion (GTV-T/IM), plus a 2, 5, 10 or 20 mm symmetrical margin, respectively. The fifth match method used a square VOI enclosing the GTV-T with a 10 mm symmetrical margin. An intensity range of [-150;150] HU was used for automatic soft-tissue matches. Bony match was retrospectively performed and compared to soft-tissue match. Residual GTV-T/IM set-up deviations in all directions were studied for each match and PTV-T margins were calculated. Additionally, stable surrogates close to GTV-N was used for the residual GTV-N set-up deviation measurements and PTV-N margin calculations. Total PTV, based on the margins calculated, was measured, by adding CTV to PTV margins to the delineated CTV for bony and GTV-T/IM + 10 mm soft-tissue matches. Additional 5 patients were included and anatomical changes were observed.

Results: All soft-tissue match methods gave similar residual GTV-T/IM set-up deviations, ranging between [-3;3] mm, resulting in [5.2;5.8] mm PTV-T margins compared to bony match with deviations between [-8:10] mm and PTV-T margins [7.4;8.6] mm. Match methods utilizing larger VOIs were more stable compared to match methods using smaller VOIs. Auto match on small targets (< 3 cm^3) was problematic, and not possible for match method 5. For 77% of the patients with lymph nodes, the main bronchi area was a suitable stable surrogate. For the remaining lateral GVT-Ns the aortic arch and the main pulmonary artery were suitable as surrogates. Soft-tissue and bony residual GTV-N set-up deviations ranged between [-8;10] and [-20;9] mm respectively resulting in PTV-N margins between [6;9.8] and [7.1;8.1] mm respectively. Mean total PTV spare with soft-tissue match was 54 cm^3. Anatomical changes, atelectasis (21%) and pneumonitis (4%) occurred randomly during the course of treatment. For the 8 patients with large anatomical changes, which required adaptive strategy, atelectasis and tumor change were the dominant reasons for adaptation.

Conclusion: Using soft-tissue match reduces the required PTV-T margins and spares healthy tissue irradiation compared to bony match. For semi-automatic soft-tissue match on the primary tumor, match within GTV-T/IM with a 10 or 20 mm margin extension used as match VOIs were most appropriate. For small tumors (< 3 cm^3), match manually on GTV-T/IM itself is advisable. The main bronchi area is a suitable surrogate primarily for centrally positioned mediastinal GTV-N. Atelectasis was the dominant anatomical change observed. Daily CBCT prevent missing significant anatomical changes and shorten the time between the observation and the adaptive strategy implementation.

Abbreviations and acronyms

2D	Two-dimensional
3D	Three-dimensional
4D	Four-dimensional
AAA	Anisotropic Analytical Algorithm
AP	Anterior – Posterior
CBCT	Cone-Beam CT
CT	Computed Tomography
$CTDI_w$	Weighted CT dose index
CTV	Clinical target volume
DOF	Degree of Freedom
DRRs	Digitally Reconstructed Radiographs
DVH	Dose-volume Histogram
FOV	Field of view
GTV	Gross tumor volume
GTV-N	Metastatic regional node(s)
GTV-T	Primary tumor
GTV-T/IM	Primary tumor with Internal Margin
HU	Hounsfield Unit
IGART	Image Guided Adaptive Radiation Therapy
IGRT	Image Guided Radiotherapy
kV	Kilo voltage
LAT	Lateral
LNG	Longitudinal
LR	Left – Right
MIP-CT	Maximum Intensity Projected CT
MU	Monitor units
MV	Mega voltage
NICE	National Institute for Health and Clinical Excellence
NSCLC	Non-Small Cell Lung Cancer
OAR	Organ at risk
OBI	On-board Imager
PRV	Planning organ-at-risk volume
PTV	Planning target volume
RMS	Root mean square
ROI	Region of Interest
RTT	Radiation Therapy Technician
SCLC	Small Cell Lung Cancer
SD	Standard deviation
SI	Superior – Inferior

TPS	Treatment planning system
VOI	Volume of Interest
VRT	Vertical
WCRF International	World Cancer Research Fund International

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1 Introduction

According to World Cancer Research Fund International (WCRF International), the most common cancer worldwide is lung cancer and it accounted for 13 % of the total number of new cases that was diagnosed in 2012.[1] Out of the two lung cancer types (Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC)), the majority of patients are diagnosed with NSCLC. The most beneficial treatment option is surgery, but the majority of the patients are not capable to undergo surgery, as a result of e.g. locally advanced disease and/or metastasis.[2] Instead these patients are treated, either with a curative or palliative intent, using external radiation, with or without concomitant chemotherapy.[2] Thus, making radiotherapy the most common treatment method for lung cancer patients.[3] Total radiation dose is usually received in fractions to minimize the healthy tissue side effects while destroying the tumor. Conventionally, radiotherapy of lung cancer is delivered with a dose between 1.8 and 2 Gy per fraction, one fraction a day and five fractions a week during seven week.[4] The choice of total dose for lung cancer patients is based on the type and stage of the cancer and several international guidelines on the management of lung cancer exist.[5,6] One of these guidelines is provided by National Institute for Health and Clinical Excellence (NICE) and it recommends a conventional fractionation and a total dose of 60-66 Gy for NSCLC patients.[4]

Pre-treatment verification of the position of targets and organs at risk (OAR) as well as correction of set-up errors is most often carried out for the majority of treatment sites, by utilization of either 2D or 3D images.[7] This is often referred to as Image Guided Radiotherapy (IGRT). When IGRT is utilized to adapt the treatment it is called Image Guided Adaptive Radiotherapy (IGART). One example of the 2D approach is set-up by comparison of bony anatomy between a reference pair of orthogonal Digitally Reconstructed Radiographs (DRRs) and a corresponding pair of plain radiographs (kV and/or MV) acquired at the linear accelerator (Linac). Utilization of Cone-Beam CT (CBCT) could however be beneficial as it provides information in 3D and allows for soft-tissue visualizing. Therefore, it is commonly used for lung cancer patients. When comparing a CBCT scan with the reference CT, different match methods can be used to receive the set-up deviation which needs to be corrected for in order to achieve optimal positioning. One of them is to match on the columna vertebralis (bony match). Since columna vertebralis most often is visible, bony match can be applied on several different tumor types. Match on bony anatomy is also sufficient for many tumors where inter- and intra-fractional organ motion is limited, such as brain tumors[8,9], where the abdomen motion, respiratory and cardiac motion does not affect the position of the brain. But for tumors in the thorax or abdomen area, motions of tumors due to respiration and surrounding organ motion make it difficult to give an accurate treatment, especially if the motion is large.[10] As a result, large uncertainties in verification and localization of the target will be added if the bony match is used.[11] To compensate for these uncertainties, larger margins are used to make sure that the target receives the planned dose. Direct match on the tumor itself could give a more accurate match for tumors in the thorax or abdomen area.[11-14] Furthermore, a direct match on the tumor would give the possibility to minimize the margins used. Margins from clinical target volume (CTV) to planning target volume (PTV), when using soft-tissue match directly on the tumor have been reported to be about 2-3 mm.[15]

Several previous studies have compared soft-tissue match to bony match for lung cancer patients and proven the benefit of matching directly on the tumor.[11-15] Yeung et al.[14] presented in their paper that by using tumor match instead of bony match the required setup margin is reduced by more than 1 cm (based on the translational shifts between bony and soft-tissue match). Purdie et al.[11] reported that the outcome of using bony anatomy as a target surrogate can be inaccurate localization and verification of the tumor.

The novelty of this project is in evaluating different, previously uninvestigated, automatic soft-tissue match methods, for both NSCLC and SCLC patients. One study, similar to the current, is the one by Grams et al, where different sizes of expanded boxes around the GTV-T for soft-tissue match were investigated.[12]

Evaluation of soft-tissue match and determination of the residual set-up deviations provides the possibility to calculate PTV margins. Ottosson et al.[16] calculated in their article CTV to PTV margins by using the van Herk formula.[17,18] Furthermore, OAR margins have also been studied and one of these studies is by McKenzie et al, who also provides an overview of different margin formulas.[19] For critical OAR there is a maximum limitation dose that is not allowed to be exceed and it is therefore of importance to calculate the OAR-margins, and create a so called planning organ-at-risk volume (PRV). At Herlev hospital for example, the dose limitation for medulla is 45 Gy and 50 Gy for medulla-PRV.

The ambition at Herlev Hospital is to proceed from daily 2D IGRT with weekly CBCT to daily CBCT with automatic soft-tissue (target) match. The results of this study are intended to provide input for the radiotherapy clinic at Herlev Hospital when shifting the match protocol from bony match to soft-tissue match. Qualitative investigation was carried out between the soft-tissue and bony match. This study is also going to be used as basis for CTV to PTV and OAR margin calculations.

Anatomical changes are of interest to analyze the effect they can have on the primary tumor (GTV-T), metastatic regional node(s) (GTV-N) and OARs and to study the common anatomical changes associated with radiotherapy for lung cancer. By acquiring daily CBCT more accurate match is achieved[11-13], and anatomical changes, such as atelectasis (collapse or closure of the lung), pneumonitis (inflammation of lung tissue) and pleural effusion (water in lungs)[18,20-21], can be discovered. Daily CBCT minimizes the risk of missing anatomical changes that might appear and disappear between the weekly CBCT scans. Møller DS et al.[23] discovered that for the 163 lung cancer patients analyzed, an adaptive strategy was indicated for 12% as a result of atelectasis, pneumonitis or pleural effusion. Møller DS et al. also presented that, for some patients, pleural effusion reoccurred during the treatment session. These anatomical changes may not just affect the dose distribution, but could also cause tumor displacement or obscure the vision of tumor if they occur close to the tumor.

This study includes two parts, a match study and an adaptive study. The main purpose of the match study was to evaluate different ways of tumor match. This was carried out by studying the different relevant structures' (medulla, GTV-T, malignant lymph nodes or surrogate

structures) residual set-up deviations, after the automatic match, and to use that for calculation of the margins required for GTV-T, GTV-N and OAR. The purpose was to:

1. Evaluate the difference between the match results from the five soft-tissue methods
2. Compare bony match to soft-tissue match
3. Qualitatively evaluate and describe the possible future restrictions that can be expected in the clinic with the soft-tissue match.
4. Calculate the required margins (OAR- and CTV to PTV margins).
5. Perform statistical analysis to study if there is a significance difference in residual GTV-T/IM between the five soft-tissue match methods and to study if there is a significance difference between GTV-N and GTV-T margins in the three directions.
6. Set up a method and protocol for soft-tissue match
7. Evaluate the PTV total volume for bony and soft-tissue match.

The aim of the adaptive study was to observe and describe the typical anatomical changes (tumor shrinkage, tumor displacement, rotations, atelectasis, pneumonitis, pleural effusion, etc.) and the timing (fraction) they happen to appear/disappear during the treatment course.

2 Soft-tissue (target)-match study

2.1 Definitions

Un-tagged CT reconstruction

4DCT is performed with the help of Varian real-time position management (RPM) system to register the respiratory motion of the patient in conjunction with the CT scan. RPM-system's role is to register a breathing curve for the patient where the patient breaths normally (free-breathing). The received respiratory motion curves represent the movement of the umbilical region during the scan, and are utilized for image reconstructions of the 4DCT reconstructions From the 4DCT the un-tagged reconstruction is then derived. This is done by dividing the breathing curve into ten breathing phases and during the CT scan the slices are divided into the ten phases to obtain the scanning area in the ten different phases. To achieve the un-tagged reconstruction these images from the ten phases are added together and the result is a blurred total image (with blurred tumor image) which indicates the tumor movement during the 10 phases. Un-tagged reconstruction image gives a true HU representation and as a result is used for both treatment planning and dose calculations. Notice that the Un-tagged image does not give a true anatomical representation since an area with air or soft-tissue can be a combination of both of them in the Un-tagged image.

GTV-T/IM

IM in GTV-T/IM stands for internal margin and is an estimation of the GTV-T taking the tumor motion into consideration. This margin takes into account uncertainties in size, shape, and position of the GTV within the patient. GTV-T/IM is delineated with the help of reconstructed

MIP-CT by using all the representations of the GTV in the ten breathing phases to create a united GTV (GTV-T/IM). [28] This GTV-T/IM is then transferred to the Un-Tagged image set, which is a time weighted reconstruction that gives a blurred image of the tumor and shows the area the tumor has been moving in during the ten breathing phases. In addition to the reconstructed MIP-CT, the oncologists at Herlev Hospital edit the GTV in all the ten breathing phases so it is a combination of the MIP-CT and single phases. The Un-Tagged image is then used for dose calculation, treatment planning and as a reference image to compare with the weekly CBCT images. The reason for using the Un-Tagged image set as a reference and not the MIP-CT is because MIP-CT did not give a true HU representation and cannot be used for dose calculations. A CBCT scan takes around 1.5 minutes to perform which makes it corresponds to a slow CT scan (Un-tagged CT) where the tumor is blurred. Since Un-tagged CT is used for both treatment planning and dose calculations it is logical to also use it for matching. If different images are used for treatment planning and matching, systematic errors can be introduced.

Reason for the chosen HU-interval for both bony and soft-tissue match

For bony match (with medulla as VOI and a margin of 2.5 cm) the current HU-interval which is used at Herlev Hospital is 50-3000. The reason for just this interval is that they studied different intervals for different patients and found that this interval covers not only the cortical bone with high HU-values, but also the soft bone with lower HU-values, around 50 HU, since the bone contains of different HU-values. This makes it possible to include the soft bone part within the 2.5 cm margin. The reason for the maximum HU-limit, 3000 is just to make sure that even the bone part with highest intensity is also included plus the fact that if some patient happens to have some implant with high intensity within this margin, it would also be included.

The reason for 2.5 cm as a margin size around the medulla is that they want to match on both the medulla and the vertebra around the medulla. Measurements showed that the distance between the middle of the medulla and outer edge of the vertebra is around 2.5 cm.

In the same way, as for bony match HU interval, the appropriate HU-interval for soft tissue is found to be between -150 and 150.

2.2 Overview of the study

Five different soft-tissue match methods were studied and evaluated by measuring the residual set-up deviation for GTV-T/IM, GTV-N and medulla. Similarly, the residual set-up deviations were also acquired for the bony match. A qualitative as well as quantitative comparison between the different match methods was carried out. CTV to PTV margins, both for primary tumor and malignant lymph nodes as well as medulla-PRV margins were calculated. Only 3DOF match procedures (both bony and soft-tissue match) were used for the residual deviation measurement and margin calculation.

The PTV volume is crucial for the extent of side effects. The total PTV volumes, based on the calculated margins for one soft-tissue match method and the bony match, was compared. This was performed to study which match method spare healthy tissue irradiation. This comparison was carried out for patients with both GTV-T and GTV-N.

Benefits and limitations of the different match methods were investigated by observing the methods' ability to match on different tumor sizes and positions, as well as to manage changes in tumor size during the course of treatment. Based on the above mentioned analyses and calculations a clinical implementation protocol for the recommended match strategy was presented (Appendix V).

2.3 Material and methods

2.3.1 Patients, immobilization and current IGART protocol

For this study a total of 23 patients (with different GTV-T and GTV-N locations (Figure 1, tables Table 1 and Table 2)) treated between January 2013 – January 2014 at Herlev Hospital, were included. Out of these 23 patients, 16 were diagnosed with NSCLC and 7 with SCLC. *Varian Clinac iX 2300* linear accelerator was used for the treatment and the majority of the patients were treated with RapidArc and the rest with IMRT.[24] Patients were immobilized by using half-body vacuum pillow, VacFix (PAR Scientific A/S, Odense, Denmark), fixed individually for each patient.

The respiratory correlated 4DCT scanning was performed for these patients using a free-breathing retrospective helical thorax protocol.[16]

At present time the margins used at Herlev Hospital are, in general, 5 mm between GTV and CTV. For the PTV and medulla-PRV a 5 mm isotropic margin is generated around the CTV and medulla, respectively.

Pretreatment positional verification, for lung cancer patients at Herlev Hospital is currently performed using a match protocol containing weekly kV CBCT and daily orthogonal (0° and 270°) 2D kV planar images. In this protocol image-guidance with CBCT is performed using Varian low-dose thorax CBCT scanning protocol.[25] The CBCT scan is compared to the reference CT scan (section 2.1)[26] and an auto-match is performed, based on medulla-PRV with a margin of 2.5 cm and HU-values between 50 – 3000. Set-up deviations are then corrected by adjusting the patient position through treatment couch shifting (3DOF, translational shifts, excluding rotations). A CBCT scan takes about 1.5 min rendering in a $CTDI_w$ (average dose in scanned volume for Perspex phantom) of 4.7 mGy.[27]

A total of 135 CBCT scans for the 23 patients were used in this study.

Table 1. Summary of patients' GTV-T locations (LUL: left upper lobe, LLL: left lower lobe, RUL: right upper lobe, RML: right middle lobe, RLL: right lower lobe, Med: mediastinum).

	NSCLC							SCLC					
GTV-T location	**Med**	**RUL**	**RLL**	**LUL**	**LUL & part of mediastinum**	**RML & part of mediastinum**	**2 GTV-T in RUL**	**RUL**	**RML**	**LUL**	**LLL**	**LUL & part of mediastinum**	**GTV-T1: RUL GTV-T2: RLL**
Patien	1	2, 10, 13, 15	6, 12	4, 5, 7, 9	3, 11	14	8, 16	19	18, 21	17	23	22	20

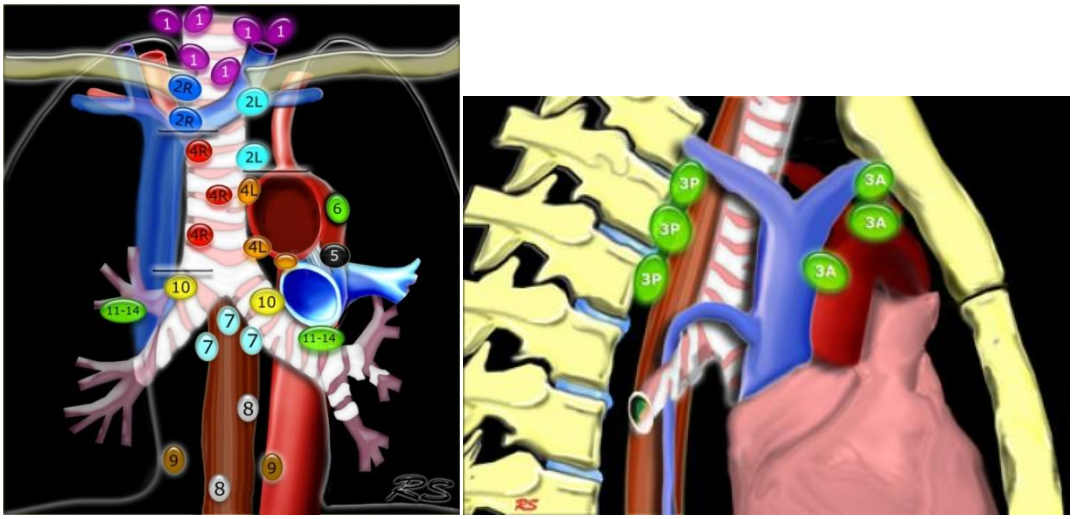

Figure 1. Regional lymph node classification for lung cancer staging adopted from the American Thoracic Society mapping scheme.[29]

Table 2. Summary of patients' GTV-N locations.

	NSCLC									SCLC					
GTV-N location	2R	3A	4R	4L	4L & 5	4R & 10R	5L & 6L	7 & 11R	6	7	4R	4R & 7	4R, 4L & 7	4R, 7 & 10R	10R	10L
Patient	12	4	1, 10, 12, 14	7	4, 9	13	7	6	1 5	8, 11, 16	23	21	19	20	18	22

2.3.2 Bony- and Soft- tissue match methods

In this study five soft-tissue match methods were evaluated. Four of these methods utilized the volume of interest (VOI) of the 4DCT defined GTV including the internal motion (GTV-T/IM, with a 2, 5, 10 or 20 mm symmetrically added margin (Figure 2A). The HU-values (intensity range) were chosen between -150 and 150. Only voxels within the selected intensity range and inside the VOI will be considered during the match. The fifth soft-tissue match method utilizes a square VOI enclosing the GTV-T with a 10 mm symmetrical margin (cranio-caudal, anterior- posterior and dexter-sinister) (Figure 2B). The intensity range within

this ROI was again between -150 and 150 HU, which means that only voxels within this range will be considered in context of the match. Bony match method was performed as described in section 2.3.1.

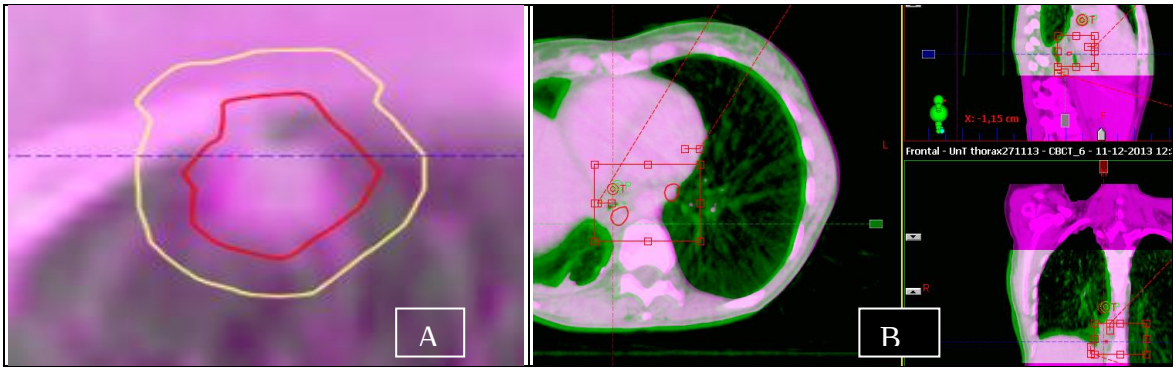

Figure 2. A: GTV-T/IM + 2 mm margin expansion. B: User-defined 3D ROI (GTV-T + 1 cm clip box)

2.3.3 Offline automatic CBCT match

In the registration software *offline review* (Varian Medical System version 8.8), CBCT scans for each patient were matched to the un-tagged reconstruction of the reference CT scan using the five different soft-tissue match methods and bony match method (section 2.3.2). Both automatic soft-tissue and bony match were performed starting from the acquisition position, where the image was acquired (alignment of the patient's skin markers (tattoos) to the lasers in the treatment room). An automatic match was performed in 3DOF (translational shifts, VRT, LNG and LAT) for bony match and in both 3DOF and 6DOF for soft-tissue match. 6DOF includes both translational shifts and rotations (pitch, roll and yaw). Pitch rotation is around LAT axis, roll rotation is around LNG axis and yaw rotation is around VRT axis. The translational and/or rotational shifts were noted for each CBCT match. After each 3DOF match, residual set up deviations for medulla (in the same cranio-caudal extension as the delineated total PTV), GTV-N and GTV-T/IM were measured as described in section 2.3.4,II and III . When measuring GTV-N and GTV-T/IM, the "*lung*" window level used for both reference CT and CBCT. For medulla deviation measurement, "*abdomen"* window level was used.

2.3.4 Measurement of residual set-up deviation after auto match

I. Medulla deviation after automatic soft-tissue match

Medulla is the most critical OAR with a dose tolerance limit of 45 Gy, not allowed to be exceeded.[30] For soft-tissue match, columna vertebralis residual set-up deviation was measured in all 3 directions (VRT, LNG and LAT). For bony match, medulla deviation was considered to be close to zero. Columna vertebralis residual deviation for soft-tissue match was measured by calculating the difference in the translational shifts between the automatic bony and soft-tissue match. This was performed using the formulas below,

$$x_{soft-tissue} - x_{bone} \qquad (1.a.)$$

$$y_{soft-tissue} - y_{bone} \quad (1.b.)$$

$$z_{soft-tissue} - z_{bone} \quad (1.c.)$$

where x, y and z are the couch shifts in the three directions (LR, SI and AP), respectively.

II. GTV-N deviation after automatic soft-tissue and bony match

The malignant lymph nodes (GTV-Ns) were not easily visible in the CBCT. Surrogate structures close to GTV-N were used to give an estimation of the deviation for GTV-N. If for example GTV-N was centrally positioned in the mediastinum, main bronchi area (bronchi) was used as a surrogate (Figure 3). For 77% of the patients bronchi was used as surrogate for GTV-N. Other surrogates utilized were trachea, descending aorta, aorta arch and pulmonary artery (Appendix II, Figure 20 - Figure 23).

The measurement of these surrogates' residual set-up deviation was carried out in the slices where PTV-(T+N) volume was present, for both transverse and sagittal plane. The transverse plane was used to measure the deviations in vertical and lateral directions while sagittal plane was used for longitudinal deviations. Measurements were performed by first performing automatic match (either bony or soft-tissue match) from the acquisition position, and thereafter manual match on the surrogate structure to minimize the residual deviation. In conjunction with the manual match a scroll on all the slices was performed to make sure that the match fits for the majority of the slices of interest. In a color blending of the reference CT (pink) and the CBCT (green), perfect match was obtained when the color turned white. The difference between the translational shifts after the automatic match and the manual match gave the GTV-N deviation. The deviation was measured in all three directions (Appendix II, Figure 24).

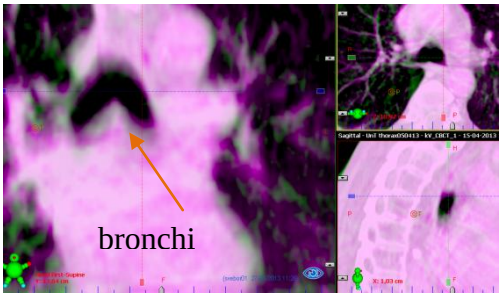

Figure 3. Main bronchi area (bronchi) as a surrogate for GTV-N

III. Measure GTV-T/IM deviation after automatic soft-tissue and bony match

a. Entire GTV-T/IM located in the mediastinum

For patient 1 the entire GTV-T/IM was located in the mediastinum which made it impossible to visualize on CBCT. For deviation measurements, carina[31] (Appendix II, Figure 25) was used as a surrogate structure for GTV-T/IM.

b. GTV-T/IM located in the lung or partly in the mediastinum

For patients with GTV-T/IM located in the lung, or partly in the mediastinum it was possible to visualize it, or part of it, on CBCT. In this case the magnitude of the maximum deviation was measured rather than measuring it in the different directions. It was studied if GTV-T/IM deviation was 1, 2, 3, 4 or 5 mm (Appendix II, Figure 26 and Figure 27). Evaluation structures (volumes) were rendered by adding symmetrical margins of 1, 2, 3, 4 and 5 mm, respectively, to GTV-T/IM in the *Contouring* module in *Eclipse* (Varian Medical Systems) treatment planning system (TPS) (Appendix II, Figure 27). Studying GTV-T/IM in two planes, the deviation could be determined. Three patients had two GTV-T/IMs (the second GTV-T/IM not used for the soft-tissue match is called GTV-T2/IM). GTV-T2/IM deviations were also measured for all match methods.

IV. Measure GTV-T/IM deviation after automatic soft-tissue and bony match for margin calculation

In section 2.3.4**, III**, GTV-T/IM residual deviation measurement included the magnitude of deviation without taking the direction of the deviation into account. To calculate CTV-T to PTV-T margin both the direction and magnitude of the deviation is needed.[32] For the patients with the entire GTV-T/IM visible (18 patients (Table 1)), GTV-T/IM residual deviation was measured in all directions by performing automatic match and observing the shift from the acquisition position to the automatic match. A manual match on GTV-T/IM was then performed to minimize the residual deviation to zero deviation. The difference between the translational shifts after the automatic match and the manual match gave the GTV-T/IM residual deviation in all three directions. One patient was excluded from the study since the treatment protocol could not be follow.

2.3.5 Set up errors and margin calculations

For each of the soft-tissue match methods residual set-up deviations were calculated for GTV-T/IM (in some cases for all GTV-T/IMs for patients with multiples GTV-T/IMs), GTV-N and medulla as described in section 2.3.4.

Residual set-up deviations for the five soft-tissue match methods were compared to evaluate the match method with the minimum residual deviation for GTV-T/IM (section 2.3.4, **III)**. GTV-T/IM (section, 2.3.4**, IV)**, GTV-N and OAR (medulla) deviations on both the three directions and 3D deviation were compared. GTV-T/IM and GTV-N deviations were also measured in all directions and in 3D. The 3D residual deviation, *d*, was obtained as,

$$d = \sqrt{dev^2{}_{vrt} + dev^2{}_{lng} + dev^2{}_{lat}} \qquad (2)$$

where *dev* is the residual deviation in the three different directions. MATLAB statistics Tool-box version 7.1 (R2010a) (The MathWorks, Natick, MA) was used to investigate if there was a match method with significantly minimal GTV-T/IM deviations (significance level $p < 0.05$). The testes performed were ANOVA (one-way) test and multiple comparison test (the

Bonferroni method)[33]. F-tests (study significant variance, significance level $p < 0.05$) were used to study significance difference between VRT, LNG and LAT residual deviations for GTV-T/IM and GTV-N.

Overall mean, M, standard deviation of the systematic set-up error,Σ, and standard deviation of the random set-up error, σ, were calculated for GTV-T/IM, GTV-N and medulla's residual set-up deviation. The statistics were performed for each soft-tissue match method and bony match. Overall mean, M was obtained by calculating the mean of all the patients' set-up deviation means. In accordance with van Herk, Σ (systematic set-up error) is defined as the standard deviation of all the patients' mean set-up error, where σ (random set-up error) is defined as the root mean square of the standard deviations of all the patients.[32] The systematic and random set-up errors calculated were used to calculate the population-based CTV to PTV margin, MG_{PTV}, using the following van Herk's margin recipe[17,18]:

$$MG_{PTV} = 2.5 \cdot \Sigma + \beta \cdot \sqrt{\sigma^2 + \sigma_P^2} - \beta \cdot \sigma_P^2 \qquad (3)$$

where β = 1.64 ensures that at least 95 % of the prescribed dose is delivered to 90 % of the patients. σ_P= 0.64 cm represents the penumbra width in the lung obtained by cumulative Gaussian.[34] $2.5 \cdot \Sigma$ account for the systematic errors, where the factor 2.5 is based on a 90 % confidence level. This will ensure that, in any single direction, CTV will be encompassed by this margin in 90% of treatment plans.

Margins for PTV (both the primary tumor and lymph-nodes) were calculated in both the 3 directions and 3D vector. To calculate the margin for medulla, McKenzie's following formula was used,[19]

$$MG_{PRV} = 2.5 \cdot \Sigma + 0.5 \cdot \sigma \qquad (4)$$

This formula is used for serial OARs or small, parallel OARs when the value of the plateau dose or the final prescription dose is unknown at the time of delineation of the OAR. A plateau dose is a dose level received for the OAR as a result of a combination of doses from the beam in all directions. An analysis was also done to study if there was significant difference between the set-up deviations in the three directions.

For bony and soft-tissue match couch shifts were subtracted for each translational dimension and 3D vector. The 3D couch shift, *D*, was calculated as,

$$D = \sqrt{(x_{soft-tissue} - x_{bone})^2 + (y_{soft-tissue} - y_{bone})^2 + (z_{soft-tissue} - z_{bone})^2} \qquad (5)$$

2.3.6 Match structure

PTV is used to ensure that 90% of the patients receive 95% of the planned dose, but when comparing CT to the CBCT image there is a need for a certain tolerance for GTV-T/IM, due to e.g. deformation of the target. A match structure with a certain size is therefore applied to GTV-T/IM to ensure that 95% of the planned dose is received. The soft-tissue match is accepted if GTV-T/IM lies inside the match structure.

2.3.7 Total PTV volume with the calculated margins

Based on the calculated CTV to PTV margins (section 2.3.5) the total PTV volume was obtained by adding the margins to the delineated CTV. This was performed in the *Contouring* in *Eclipse* (Varian Medical Systems), where also the PTV volumes were measured from the automatically calculated volumes in *Eclipse*. The measurement of PTV was performed on the initial CT for the patients with both the primary tumor and lymph nodes. The measurement was performed for the recommended soft-tissue match method to use in clinic, and for bony match procedure. For patient 26 (section 3, Table 8) a comparison in total PTV between all match methods was performed.

2.4 Results

2.4.1 Offline automatic CBCT match

2.4.1.1 Soft-tissue match

The five soft-tissue match methods gave similar match results with GTV-T/IM residual deviations (measured according to section 2.3.4, **III**) ranging between 0-3 mm and a mean GTV-T/IM residual deviation of 2 mm (Figure 4). The 3 mm deviation was mostly for patient 5 due to tumor deformation. For patient 9 and 18 the GTV-T was small, not attached to the thoractic wall and shrank during the treatment. This combination made it impossible to use the match method with a 10 mm box around GTV-T. Match with GTV-T/IM+2 mm and GTV-T/IM+5 mm gave varying match results (different match results when match the same CBCT with same match method) for the same CBCT for patient 9. Match with the other match methods gave also varying results but was less varying compared to the methods with smaller VOI. For larger tumors, tumors attached to the thorax wall or with a part in the mediastinum the soft-tissue match was stable and all soft-tissue match methods gave similar results.

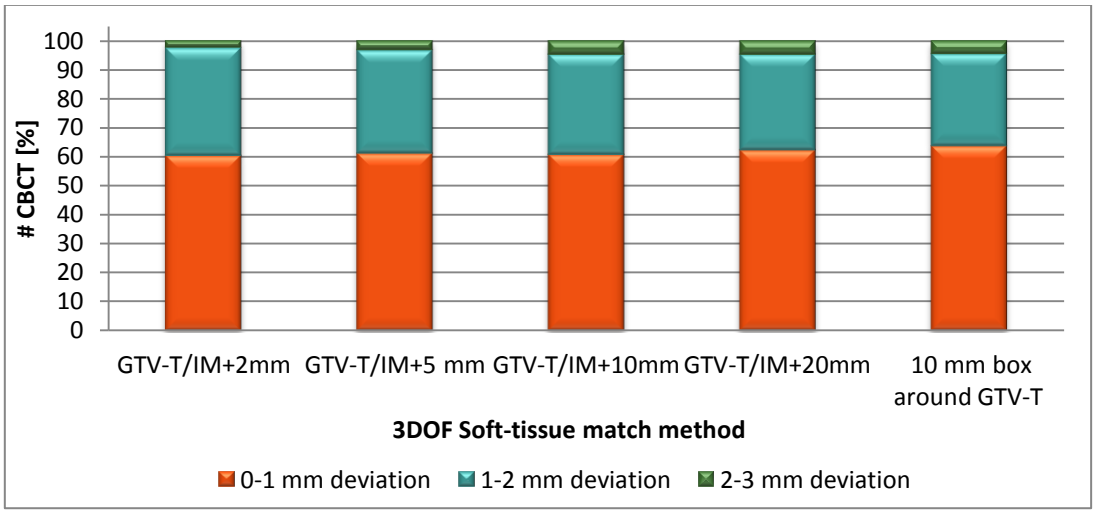

Figure 4. GTV-T/IM residual deviation after soft-tissue match for the five different soft-tissue match methods.

That Maximum residual deviation for GTV-T2/IM after soft-tissue match was 3 mm (**Figure 5**), which was the same as for GVT-T/IM (Figure 4).

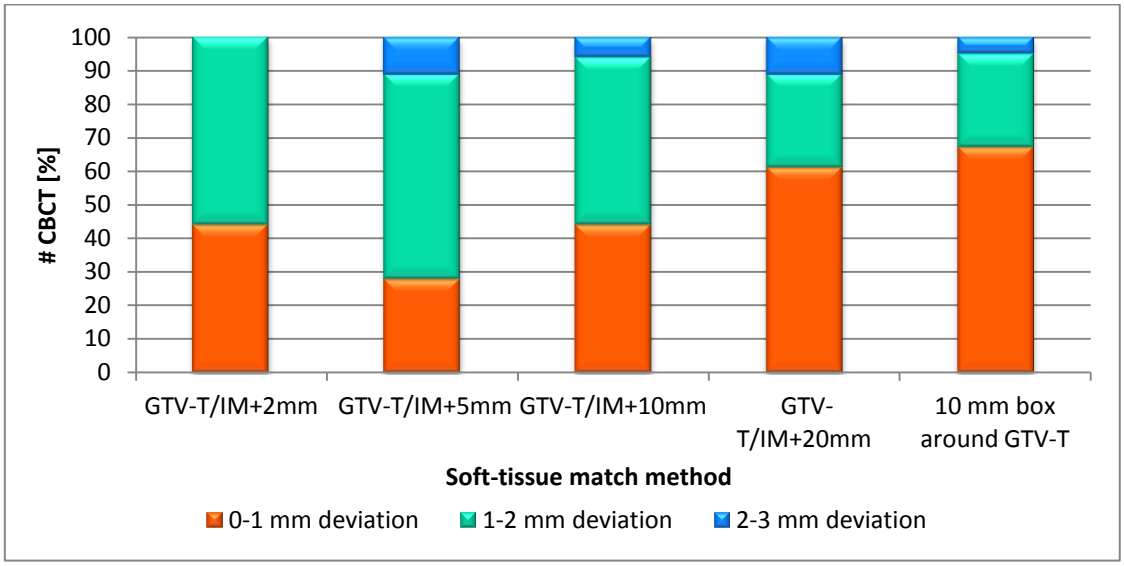

Figure 5. GTV-T2/IM residual deviation after soft-tissue match for the five different soft-tissue match methods

The four automatic soft-tissue match methods with an expanded GTV-T/IM volume were quick to perform (few seconds), while the method with the box around GTV-T required about 3-4 minutes since the box had to manually be set to 1 cm in all planes.

Rotations in all directions were within 5° with just 2 CBCT over 5° in roll rotation. For approximately 80% of the matches the rotation was between 0-2° in all directions (Figure 6). All soft-tissue match methods gave similar rotation results.

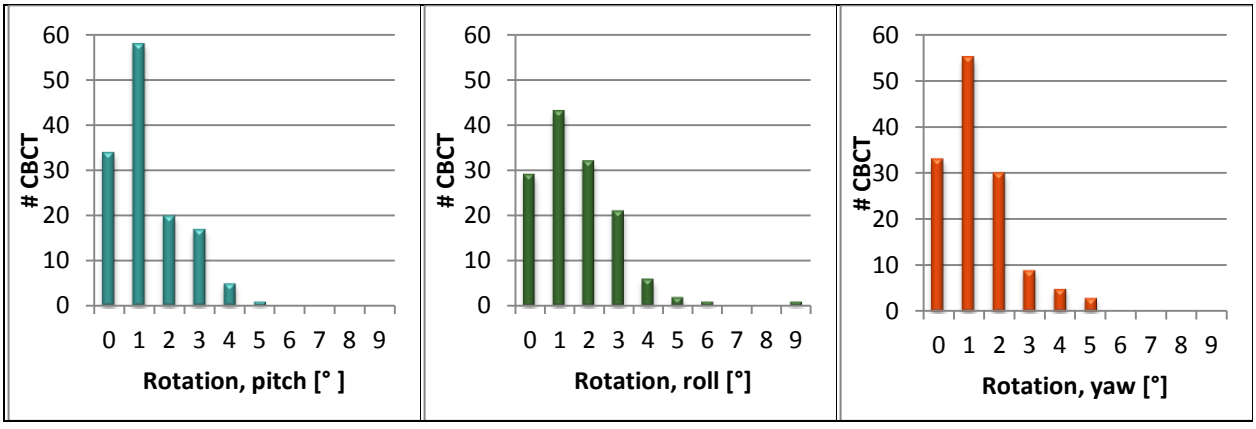

Figure 6. Rotations (Pitch, Roll, Yaw) for the 6DOF GTV-T/IM + 10 mm soft-tissue match procedure.

2.4.1.2 Bony match

Bony match was possible to perform for all patients. For patients 6 and 8 the residual GTV-T/IM deviations after bony match were the same as when soft-tissue match was used. GTV-T/IM deviation larger than 5 mm, with bony match, was seen for patients 10 and 12 (Appendix II, Figure 28). Residual GTV-T/IM deviations after bony match (measured

according to section 2.3.4, **III**) are presented in Figure 7. Maximum Residual GTV-T2/IM deviation obtained for GTV-T2/IM with bony match was 6 mm (**Figure 8**).

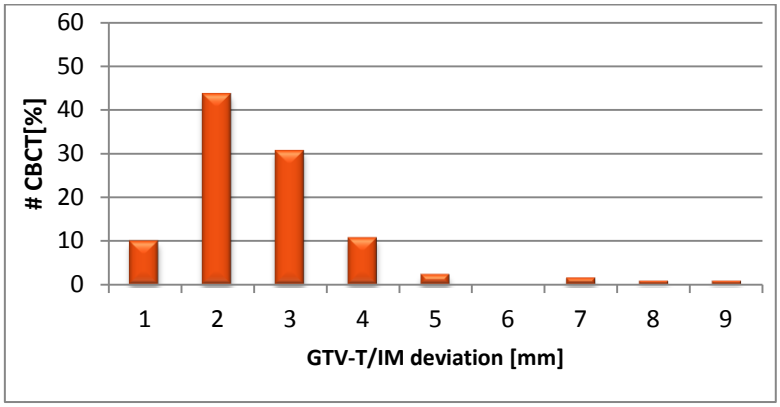

Figure 7. GTV-T/IM residual deviation after bony match procedure.

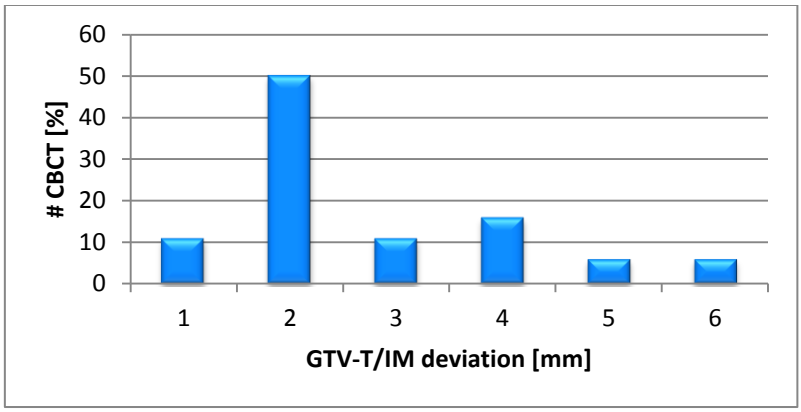

Figure 8. GTV-T2/IM residual deviation after bony match procedure.

2.4.2 Set up errors and margin calculations

A summary of the 3D couch shifts differences between soft-tissue match and bony match (using equation 5) shows that the mean shift difference was 5 mm and was larger than 5 mm for 22% of the matched CBCTs (Table 3).

Table 3. Summary of 3D couch shifts (mm) between soft-tissue match procedure (GTV-T/IM+20mm) and bony match procedure.

3D couch shifts differences	
Mean ± SD	5.0 mm ± 3.3
Maximum	10 mm
D = 0-2 mm	42.3%
$2 < D < 5$	35.4%
$D \geq 5$ mm	22.3%

Maximal 3D couch shifts differences between soft-tissue match (GTV-T/IM+20mm) and bony match was 10 mm (**Figure 9**). 3D couch shifts differences between the other soft-tissue match methods and bony match gave similar results.

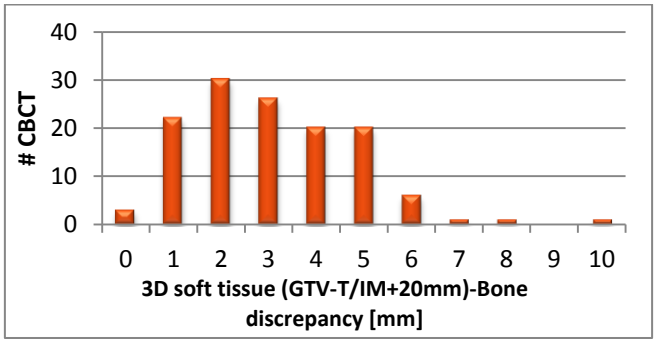

Figure 9. 3D soft tissue (GTV-T/IM+20mm)-Bone discrepancy

The calculated medulla-PRV margins using equation 4 for soft-tissue match show that the margins ranged between 4 and 5 mm in all directions and 3D margins were approximately 4 mm for all match methods (Table 4). Systematic set-up errors, Σ, and random set-up errors, σ, based on population measurements used to calculate medulla-PRV margins for all soft-tissue match methods, were also calculated. Systematic set-up errors were around 1.5 mm in VRT and LNG directions, and around 1.3 mm in LAT direction, for all soft-tissue match methods. Random set-up errors ranged between 1.2 – 2.2 mm in all three directions (Appendix III, **Fel! Hittar inte referenskälla.**).

Table 4. Medulla-PRV margins when soft-tissue match procedure is used. Medulla-PRV margin is based on the difference in couch shifts between soft-tissue match and bony match procedure.

	Medulla-PRV Margin	VRT [mm]	LNG [mm]	LAT [mm]	3D [mm]
Soft-tissue match method	GTV-T/IM+2mm	5.0	5.1	4,5	4.2
	GTV-T/IM+5mm	4.5	5.4	4.4	4.0
	GTV-T/IM+10mm	4.7	5.1	4.0	4.1
	GTV-T/IM+20mm	4.1	5.1	3.6	3.5
	1 cm box around GTV-T	4.0	5.0	3.6	3.9

Residual deviations for GTV-T/IM after soft-tissue match (measured according to section 2.3.4, **IV**) with GTV-T/IM+5 mm match method shows that for soft-tissue match the deviations ranged between -3 and 3 mm in VRT and LNG directions. Deviations in LAT direction was between -3 and 2 mm. GTV-T/IM residual deviations for the remaining soft-tissue match methods are presented in Appendix II, Figure 31, and are similar to the results of GTV-T/IM+5 mm match method. GTV-T/IM deviations for bony match were larger than soft-tissue match in all directions (Figure 10).

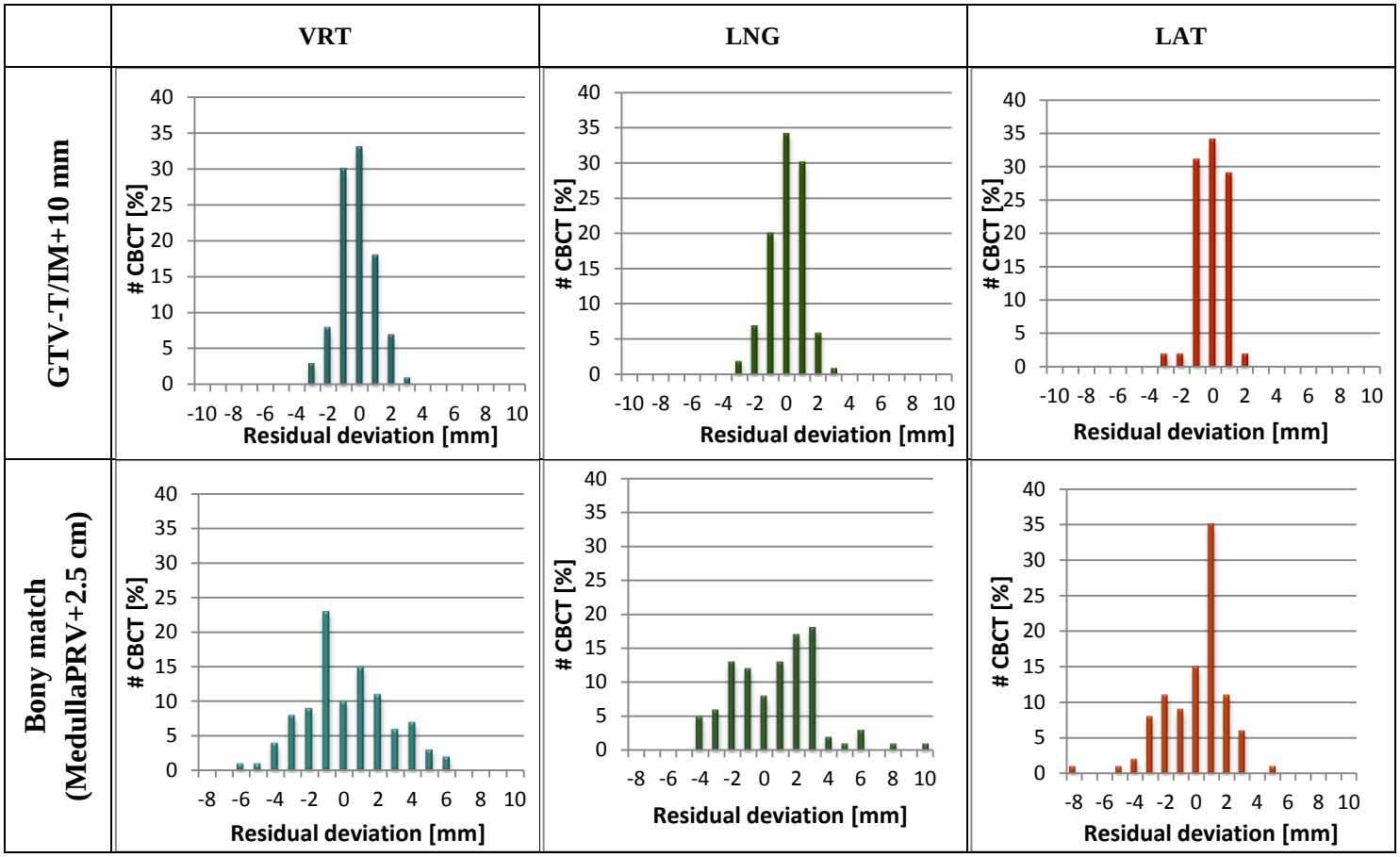

Figure 10. GTV-T/IM residual deviation after soft-tissue match (utilizing GTV-T/IM plus a 5 mm symmetrical margin, and bony match.

The calculated CTV-T to PTV-T margins using equation 3 for soft-tissue and bony match procedure show that the required CTV to PTV margins are 2-3 mm smaller with soft-tissue compared to bony match (Table 5). Systematic set-up errors,Σ, were calculated and were around 0.6 mm for all soft-tissue match methods in all the three directions. Random set-up errors, σ, were around 1 mm for all soft-tissue match methods. For bony match both systematic and random set-up errors were twice as much as soft-tissue match methods values (Appendix III, **Fel! Hittar inte referenskälla.**).

Table 5. PTV-T margins when match procedure is used to account for residual deviations in GTV-T/IM. PTV-T margins are based on Equation 3.

	CTV-T to PTV-T Margin	VRT [mm]	LNG [mm]	LAT [mm]	3D [mm]
Match method	Soft-tissue: GTV-T/IM+2mm	5.2	5.6	5.2	5.6
	Soft-tissue: GTV-T/IM+5mm	5.2	5.8	5.2	5.3
	Soft-tissue: GTV-T/IM+10mm	5.4	5.8	5.3	5.4
	Soft-tissue: GTV-T/IM+20mm	5.3	5.7	5.2	5.4
	Soft-tissue: 1 cm box around GTV-T	5.5	5.6	5.2	5.4
	Bony: Medulla-PRV+2.5 cm	7.9	8.6	7.4	7.3

Residual deviations for GTV-N in all three directions after soft-tissue (GTV-T/IM+ 20 mm) and bony match show that the deviations in all directions are similar for both bony and soft-tissue match (Figure 11). GTV-N residual deviations for the remaining soft-tissue match methods were similar to GTV-T/IM+ 20 mm.

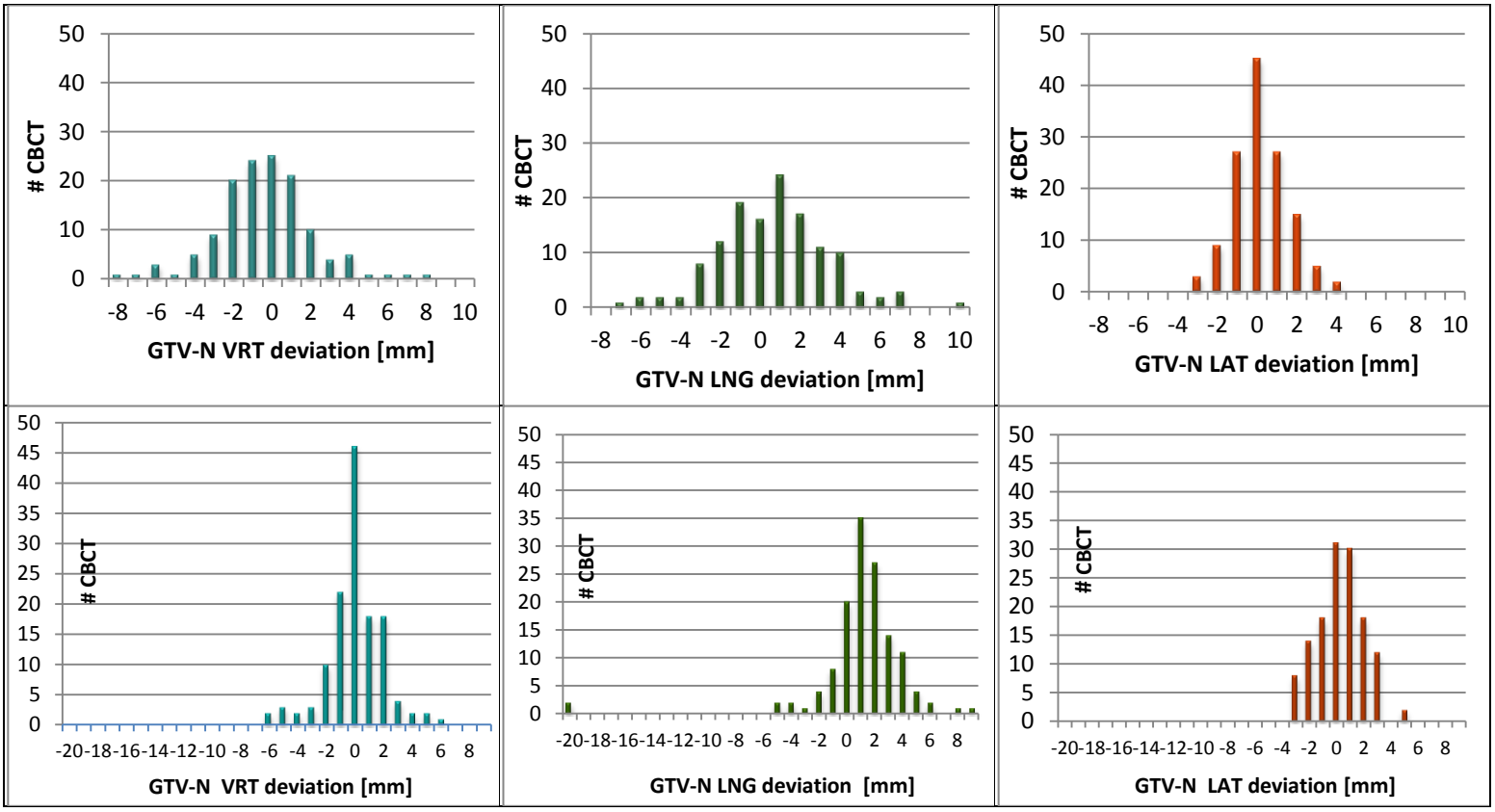

Figure 11. GTV-N residual set-up deviation after soft-tissue GTV-T/IM+20mm match procedure (above) and bony match procedure (under).

PTV-N margins for soft-tissue and bony match show that margins in VRT and LNG directions are smaller for bony match compared to soft-tissue match. On the other hand there is a margin reduction in LAT direction for almost all soft-tissue match methods compared to bony match (Table 6). Calculated systematic set-up errors,Σ, for 3D vector, were around 1.7 and 1.3 mm for soft-tissue and bony match procedure respectively. Random set-up errors, σ, for 3D vector, were around 1.5 and 2 mm for soft-tissue and bony match procedure respectively (Appendix III, **Fel! Hittar inte referenskälla.**).

Table 6. PTV-N margins when match is used to account for residual deviations in GTV-N. PTV-N margin is based on Equation 3.

	CTV-N to PTV-N Margin	VRT [mm]	LNG [mm]	LAT [mm]	3D [mm]
Match method	Soft-tissue: GTV-T/IM+2mm	9.8	8.9	7.1	8.3
	Soft-tissue: GTV-T/IM+5mm	9.5	9.2	6.8	8.5
	Soft-tissue: GTV-T/IM+10mm	9.6	9.3	6.3	8.4
	Soft-tissue: GTV-T/IM+20mm	9.1	9.2	6.0	8.1
	Soft-tissue: 1 cm box around GTV-T	9.5	9.2	6.5	8.3
	Bony: Medulla-PRV+2.5 cm	7.6	8.7	7.1	7.5

All statistical analyses are found in Appendix IV.

Appendix III – Calculated systematic and random set-up errors

Table 9. Systematic set-up error,Σ, and random set-up error, σ, based on population measurements to calculate medulla-PRV margins for all soft-tissue match methods.

		Σ [mm]	σ [mm]	Σ [mm]	σ [mm]	Σ [mm]	σ [mm]	Σ [mm]	σ [mm]
Match method		**VRT [mm]**		**LNG [mm]**		**LAT [mm]**		**3D [mm]**	
	Soft-tissue: GTV-T/IM+2mm	1.67	1.68	1.63	1.95	1.54	1.33	1.34	1.74
	Soft-tissue: GTV-T/IM+5mm	1.48	1.60	1.72	2.13	1.47	1.39	1.25	1.69
	Soft-tissue: GTV-T/IM+10mm	1.58	1.52	1.64	2.11	1.35	1.28	1.29	1.69
	Soft-tissue: GTV-T/IM+20mm	1.38	1.22	1.64	1.97	1.19	1.22	1.14	1.36
	Soft-tissue: 1 cm box around GTV-T	1.35	1.32	1.55	2.24	1.21	1.18	1.26	1.50

Table 10. Systematic set-up error,Σ, and random set-up error, σ, based on population measurements to calculate CTV-T to PTV-T margins for all the match methods.

		Σ [mm]	σ [mm]	Σ [mm]	σ [mm]	Σ [mm]	σ [mm]	Σ [mm]	σ [mm]
Match method		**VRT [mm]**		**LNG [mm]**		**LAT [mm]**		**3D [mm]**	
	Soft-tissue: GTV-T/IM+2mm	0.521	1.07	0.702	0.968	0.546	0.744	0.662	0.979
	Soft-tissue: GTV-T/IM+5mm	0.522	1.08	0.782	0.906	0.542	0.735	0.570	0.949
	Soft-tissue: GTV-T/IM+10mm	0.598	1.08	0.788	0.911	0.561	0.766	0.618	0.978
	Soft-tissue: GTV-T/IM+20mm	0.567	1.11	0.677	1.22	0.541	0.898	0.595	1.07
	Soft-tissue: 1 cm box around GTV-T	0.639	1.11	0.680	1.04	0.540	0.891	0.580	1.02
	Bone: Medulla-PRV+2.5 cm	1.46	2.02	1.67	2.28	1.33	1.54	1.19	2.04

Table 11. Systematic set-up error,Σ, and random set-up error, σ, based on population measurements to calculate CTV-N to PTV-N margins for all the match methods.

		Σ [mm]	σ [mm]	Σ [mm]	σ [mm]	Σ [mm]	σ [mm]	Σ [mm]	σ [mm]
Match method		**VRT [mm]**		**LNG [mm]**		**LAT [mm]**		**3D [mm]**	
	Soft-tissue: GTV-T/IM+2mm	2.24	1.76	1.84	2.13	1.26	1.29	1.68	1.54
	Soft-tissue: GTV-T/IM+5mm	2.15	1.70	1.94	2.15	1.13	1.22	1.77	1.46
	Soft-tissue: GTV-T/IM+10mm	2.18	1.61	1.97	2.15	0.946	1.21	1.74	1.54
	Soft-tissue: GTV-T/IM+20mm	1.99	1.57	1.97	2.05	0.830	1.22	1.62	1.55
	Soft-tissue: 1 cm box around GTV-T	2.18	1.54	1.92	2.23	1.03	1.19	1.70	1.53
	Bone: Medulla-PRV+2.5 cm	1.40	1.52	1.63	2.58	1.23	1.28	1.29	2.08

Appendix IV – Statistical analyses Based on the analyses and above calculations a clinical implementation protocol for the recommended match strategy was presented (Appendix V).

2.4.3 Match structure

The size of the match structure is determined with the help of the GTV-T/IM residual set-up deviations obtained after the automatic soft-tissue match (Figure 4). Based on the results in Figure 4 it is seen that for 95% of the patients GTV-T/IM residual deviations will lie within 0-2 mm. Choosing a match structure of 2 mm around GTV-T/IM ensures therefore that for at least 95% of the patients GTV-T/IM will lie within the 2 mm match structure after the automatic soft-tissue match.

2.4.4 Total PTV volume with the calculated margins

PTV-total volume is a sum of PTV-T and PTV-N. The results for bony and soft-tissue (GTV-T/IM + 10 mm) match procedures indicate that if the calculated margins based on each match procedure are used, larger margins are required if bony match is used compared to soft-tissue match. Therefore, larger volumes would be included in the plan. As a result larger volumes will be irradiated. (Figure 12 and Table 7). Note also that this is due to the fact that bony match procedure results in a significantly larger PTV-T (Figure 13 and Table 7).

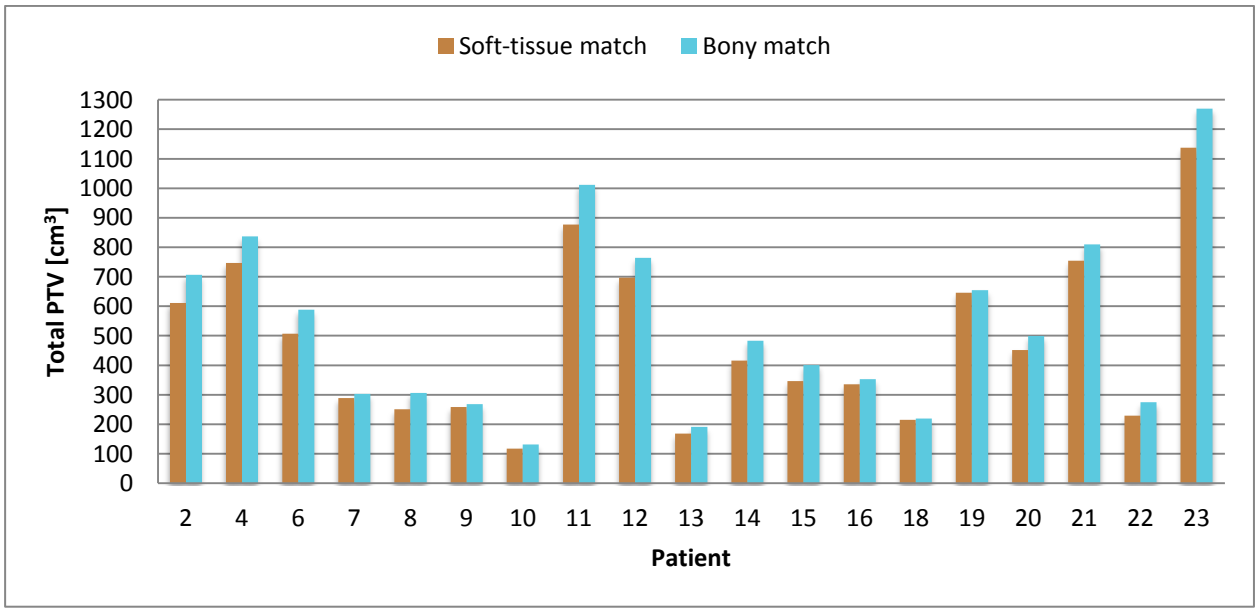

Figure 12. Total PTV for bony and soft-tissue (GTV-T/IM + 10 mm) automatic match procedure.

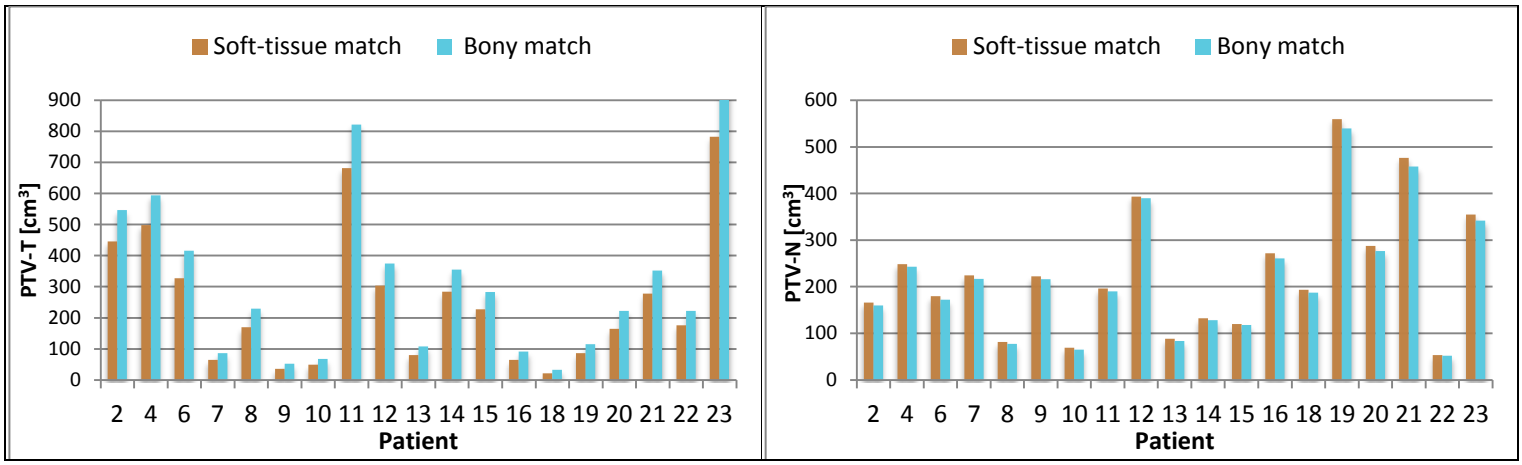

Figure 13. PTV-T and PTV-N for bony and soft-tissue (GTV-T/IM + 10 mm) automatic match procedure.

Table 7. Total measured PTV volume for patient 26, based on the CTV to PTV margins calculated for all match methods

Match method	PTV-T [cm^3]	PTV-N [cm^3]	Total PTV [cm^3]
Soft-tissue: GTV-T/IM+2mm	69.9	147.2	217.1
Soft-tissue: GTV-T/IM+5mm	69.9	147.2	217.1
Soft-tissue: GTV-T/IM+10mm	69.9	142.3	212.2
Soft-tissue: GTV-T/IM+20mm	69.9	136.4	206.3
Soft-tissue: 1 cm box around GTV-T	73.1	147.2	220.3
Bony: Medulla-PRV+2.5 cm	96.7	135.9	232.6

2.5 Discussion

The results of this study show no significance difference between the five different soft-tissue match methods in the residual GTV-T/IM set-up deviations (Figure 4, Figure 31, and Appendix IV). GTV-N residual deviations was similar between the match methods and the systematic and random set-up errors was close to each other as well (**Fel! Hittar inte referenskälla. − Fel! Hittar inte referenskälla.**). For large tumors all methods were able to give an accurate match despite the tumor shrinkage. This agrees with Grams et al.[12] report which indicates no effect on the obtained match results reliability due to tumor volume changes. Based on just these results it makes no difference which soft-tissue match method is selected. On the other hand match using the 1 cm box around GTV-T took more time to perform compared to the rest of four match methods; due to the fact that a manual measuring of the box had to be performed in all three directions. This means that if this method is used, 3-4 extra minutes will be added to the treatment session in order to account for the time to draw the 1 cm box around GTV-T in all the three planes.

For tumors < 3 cm^3 (patient 9 and 18) soft-tissue match using a box was not possible, and was not stable for the other soft-tissue match methods. This was due to two reasons. The first reason was the size of GTV-T and its close intensity to the lung tissue. An advisable solution is to manually match on the GTV-T/IM itself. The second reason was the large shrinkage of

the already small GTV-T during the treatment, finally resulting in the tumor not possible to detect. In this case further investigations have to be done to study if a surrogate close to GTV-T to match on is a solution or if larger margins around the GTV-T is to be used and in that case performing a match in a larger ROI.

All calculations for patient 18 were excluded due to large anatomical changes (Figure 29 and Figure 30). If this patient would have been included, the residual deviation would be a combination of the anatomical change (GTV-T displacement) and set-up deviation.

Soft-tissue match method using small margins around GTV-T/IM (2 and 5 mm volume extension) is not preferable. In the case of tumor deformation or tumor displacement the match software will have problems identifying the structure edges. This can probably be a result of structure edges lying outside the defined match area. This will result in non-stable match results.

Based on the results automatic soft-tissue match on the primary tumor, match within GTV-T/IM with a 10 or 20 mm margin extension used as match VOIs were most appropriate. Further investigation between GTV-T/IM with 10 and 20 mm margin extension methods can be performed to study the total PTV volume. This was performed only for patient 26 because of limited project time. The results for this patient show that the minimum volume was obtained for GTV-T/IM with 20 mm margin extension (

Table 7) with 6 cm^3 difference in PTV volume between GTV-T/IM with 10 margin and GTV-T/IM with 20 mm margin extension. Grams et al.[12] presented that automatic match using a 1-2 cm ROI encompassing PTV and including PTV as the structure VOI was most compatible with a physician's manual match (golden standard).

For the 23 patients included in the match study it was just patient 1 with obscured GTV-T (GTV-T in mediastinum) and carina was a stable surrogate to use. Different surrogates close to the GTV-N was used to measure the GTV-N residual deviations. For patients with just GTV-N the main bronchi area is a suitable surrogate to match on, primarily for centrally positioned mediastinal GTV-Ns. Depending on the position of GTV-N different surrogates can be used and for this study the five different surrogates used was stable and easy to visualize and match on. Further investigations have to be done to study how these surrogates can be used to match on, either automatic or manual. Investigations can be carried out by delineating the surrogate (by an oncologist) on the Un-tagged CT used for the match. A surrogate with margin extension as a match VOI can be studied, the same way as the first four soft-tissue match methods. Since it was easy to manually match on the surrogates used, a manual match can be performed instead and in this case no external margin is needed around the surrogate.

The results of this study show also a clear benefit when using soft-tissue match compared to bony match in form of smaller residual set up deviations for GTV-T/IM (Figure 10) and as a result a decrease of CTV-T to PTV-T margins with about 3 mm in VRT and LNG directions, and 2 mm in LAT direction (Table 5). This result agrees with previous reports which reported

that using bony as a surrogate for lung cancer is not advisable and will cause large errors in verification of target.[11-14] as over 20% of bony matched introduced ≥ 5 mm differences when compared to the automatic soft-tissue match for this study. This difference agrees with the results obtained by Grams et al12 who reported the same couch difference and same percentage as in this study between manual target match and automatic bony match. Purdie et al.[11] on the other hand presented the same 3D couch difference between manual target match and bony match for 60% of all treatment fractions for 28 NSCLC patients treated with stereotactic radiotherapy.

Residual GTV-N deviations were similar for the bony and soft-tissue match methods (

Figure 11), but with maximum residual deviation in LNG direction when bony match was used (20 mm). Deviations were smaller in LAT direction because respiratory movement is most likely less in LAT direction. CTV-N to PTV-N margins minimized with about 2.2 mm in VRT direction and 0.5 mm in LNG direction but increased with about 1.1 mm in LAT direction when bony match was used compared to soft-tissue match (Table 6). The reason for smaller margins with bony match was because the GTV-N surrogate used the most was main bronchi area (77%) and bronchi area is close to medulla compared to the main target where the distance between bronchi area and main target varies depending on the target position. The total PTV volume calculation for bony and soft-tissue match would show which match method that really spare healthy tissue the most. PTV volume comparison between soft-tissue (GTV-T/IM + 10 mm) and bony shows that PTV-N was larger when soft-tissue was used (Figure 13). But a clear irradiation spare of healthy tissue was shown when soft-tissue match was used (Figure 12). The reason is because the difference in PTV-T (mean 61 cm^3 smaller with soft-tissue match) is larger compared to the difference in PTV-N (mean 7 cm^3 smaller with bony match). Mean total PTV spare with soft-tissue match was 54 cm^3 compared to bony match. The only two observed benefits gained from bony match were stable surrogate (columna vertebra) to match on which was visible and unlikely to change shape during the treatment, and similar GTV-T/IM residual deviation to soft-tissue match (patient 6 and 8) when the tumor lied close to medulla. Considering all the benefits from using soft-tissue match [more accurate match, smaller GTV-T/IM residual deviations, smaller PTV-T margins and smaller total PTV (sparing healthy tissue)] it is recommended to use soft-tissue match instead of bony match for lung cancer.

The PTV-T margins obtained when soft-tissue match was used were around 5 mm (Table 5) which was 2-3 mm larger than Grills results.[15] Grills article included stereotactic lung radiotherapy with daily CBCT. The patients on Grills study were immobilized with body frame (SBF) or an alpha-cradle and with an external abdominal compression if the tumor motion was > 5 mm. Grills calculated the PTV-T margins by first match automatically on the target with a “best fit” match that assumes zero GTV-T residual deviation. A second CBCT was performed to measure any residual GTV-T error and calculate PTV-T margin. For the GTV-T/IM residual deviations measured in this study there was no significance difference in variance between the three directions, for all the soft-tissue match methods (Appendix IV, Table 13). For this reason a 5.5 mm 3D symmetric PTV-T margin around CTV-T is recommended (Table 5).

Results of soft-tissue calculated PTV-N shows that PTV-N in VRT and LNG directions are close to each other, but differ from the margin in LAT direction (Table 6). Further, F-tests show that LAT GTV-N residual deviations variance differed from the other directions (Appendix IV, Table 12). If soft-tissue match with GTV-T/IM with 10 or with 20 mm margin extension is to be used it is recommended to have the same PTV-N margin in VRT and LNG directions, 9.4 mm, and a PTV-N margin of 6.3 mm in LAT direction.

Medulla-PRV margins for soft-tissue match were around 5 mm in VRT and LNG direction, and around 4 mm in LAT direction (Table 4). These values did not exceed the symmetric 5 mm medulla-PRV margin used at Herlev Hospital at present time and agrees with the 4.6 mm margin represented in McKenzie's article.[19]

Results from 6DOF soft-tissue match demonstrate that for approximately 80 % of the matches the rotation was between 0-2° in all directions. This agrees with the study by Ottosson et al.[16] where the rotations were reported to be < 5°.

Out of the 23 patients included in the study, 3 patients had two GTV-Ts separated from each other. When match on one of them the residual deviation for the second GTV-T/IM did not exceed 3 mm (around 90% of the matches lied within 2 mm). For the match on GTV-T/IM a match structure of 2 mm means that GTV-T/IM will lie within the 2 mm match structure for 95% of the patients after the automatic soft-tissue match. If the same match structure is used for the second GTV-T it will ensure that for 90% of the patients GTV-T/IM will lie within the match structure. It is therefore worth investigating, for clinical use, more patients with more than one GTV-T to decide if the same match structure is to be used for all GTV-Ts, but with different accepted confidence levels or if different match structures are to be used for the GTV-T matched on and the other GTV-Ts but with the same confidence level (e.g. 95%).

For patients with more than one GTV-T it is important to make clear which GTV-T/IM to match on.

When analyzing the CBCT the actual total number of the CBCT-scans was 144 but it was not possible to analyze 9 of them due to some technical problems which prevent the CBCT-scan. Instead the RTT took 2kV plan images since they could still match on the bony structure of the columna vertebralis. If daily CBCT are to be used it is recommended to have a backup solution to match if some technical problems occur with CBCT.

Using CBCT allows soft-tissue visualization and thus allows the anatomical changes to be observed. CBCT gives information about the tumor positions. Since a CBCT-scan takes about 1.5 minutes information about the tumor motion is possible to obtain. For patient 10 for example bony match in fraction 11 was not stable due to a rotation > 5°. With the help of CBCT it was observed that the right arm was about 1.5 cm lower than the intended position.

3 Adaptive study

3.1 Overview of the study

The aim of the adaptive study is to investigate the typical anatomical changes for lung cancer and study if there is a systematic pattern in the appearance/disappearance of these changes during the treatment course. This was investigated by observing both anatomical changes and tumor changes for the weekly CBCTs. Significant anatomical changes where an adaptive strategy was required were also studied.

3.2 Material and methods

3.2.1 Patient group

For all 23 patients, included in the soft-tissue match study (section 2) anatomical changes were studied during the course of treatment. Besides patient 2, 17 and 23 who received a rescan, additional 5 NSCLC/SCLC patients (patient number 24 – 28) that had performed CT rescans during their course of treatment between October 2012 and January 2014 were also included in the adaptive study (Table 8). For patients 23 and 27 the GTV-T shrinkage was seen already before the treatment course started. The reason for this shrinkage has not been investigated.

Table 8. Summary of rescanned patients.

Patient	**2**	**17**	**23**	**24**	**25**	**26**	**27**	**28**
GTV-T Location	RUL	LUL	LLL	RML & RLL	Non GTV-T. Mediastinal GTV-N	RUL	LUL and part of the mediastinum	RLL and part of the mediastinum
Reason for rescan	Large GTV-T shrinkage, deformation and displacement as a result of loosening from thoractic wall. Pneumonitis & atelectasis	Mediastinum and tumor displacement as a result of atelectasis disappearance	GTV-T shrinkage in one side and growth in another side. Pneumonitis and atelectasis which results in tumor displacement	Bloated breasts	Mediastinum displacement as a result of atelectasis	GTV-T displacement	Mediastinum displacement as a result of GTV-T shrinkage	Mediastinum displacement as a result of atelectasis disappearance
Time for rescan	Anatomical change seen in fraction 11, rescan at fraction 21	Anatomical change seen in fraction 1, rescan at fraction 8	Anatomical change seen in fraction 1, rescan at fraction 10	Anatomical change seen in fraction 1, rescan fraction 9	Anatomical change seen in fraction 16, rescan at fraction 20	Anatomical change seen in fraction 11, rescan at fraction 14	Anatomical change seen in fraction 1, rescan at fraction 7	Anatomical change seen in fraction 11, rescan at fraction 17

3.2.2 Geometrical and anatomical changes

A total of 177 weekly acquired (135 for match study patients (section 2) and 42 for the additional 5 patients (section 3.2.1) CBCT images were analyzed in order to find the anatomical changes during the courses of treatment. Anatomical changes studied were tumor shrinkage, growth, deformation and/or displacement, pleural effusion, atelectasis and pneumonitis. The time of occurrences and disappearances of anatomical changes were identified. For this purpose, the registration software Offline Review, v.10.0 (Varian Medical Systems) was utilized.

3.3 Results

3.3.1 Geometrical and anatomical changes

The appearance and disappearance time for the anatomical changes in terms of atelectasis and pneumonitis are demonstrated in Figure 14 and Figure 15. Note that atelectasis is the predominant anatomical change (**Figure 16**) and both changes have no systematic pattern in the way they appear/disappear. Target anatomical changes over time (shrinkage, growth, deformation and/or displacement) were observed for 71% of the studied patients (Figure 14, Figure 15 and Figure 17). Target shrinkage was observed for 50% of the studied patient group, make it the dominant tumor anatomical change (Figure 18). Examples of some of the anatomical changes observed are illustrated in Appendix II, **Figure 32** and Figure 33.

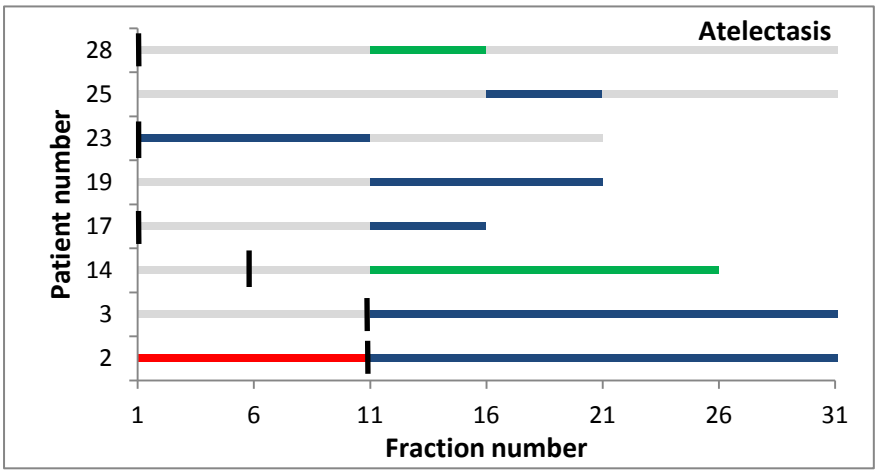

Figure 14. Time of occurrence and disappearance for atelectasis. The bar starts with the first CBCT (fraction 1) and ends with the last CBCT performed independent of the total number of fractions. Blue starts at the fraction when the atelectasis appeared. Green represents fraction when the atelectasis disappeared. Red represents failure in performing the planned CBCT due to technical problems. The vertical lines in black represent the fraction when GTV-T anatomical change (tumor shrinkage, growth, deformation and/or displacement) was observed for each patient.

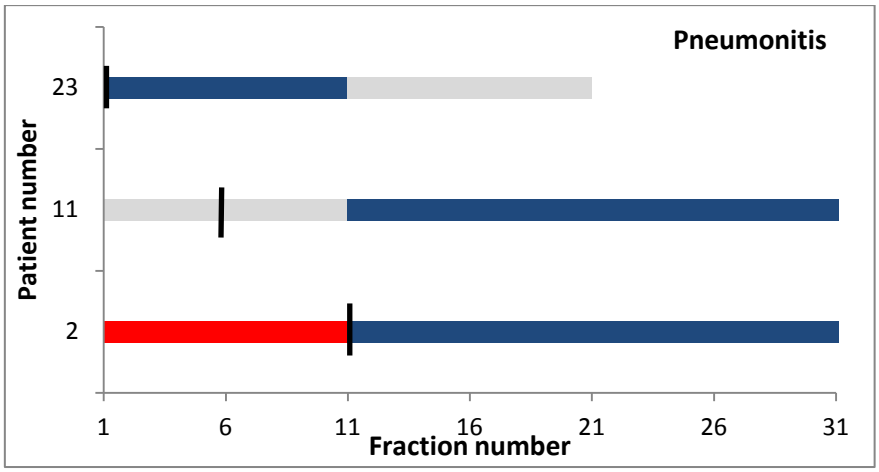

Figure 15. Occurrence and disappearance time for pneumonitis. The bar starts with the first CBCT (fraction 1) and ends with the last CBCT performed independent of the total number of fractions. Blue starts at the fraction when the pneumonitis appeared. Red represents failure in performing the planned CBCT due to technical problems. The vertical lines in black represent the fraction when GTV-T anatomical change (tumor shrinkage, growth, deformation and/or displacement) was observed for each patient.

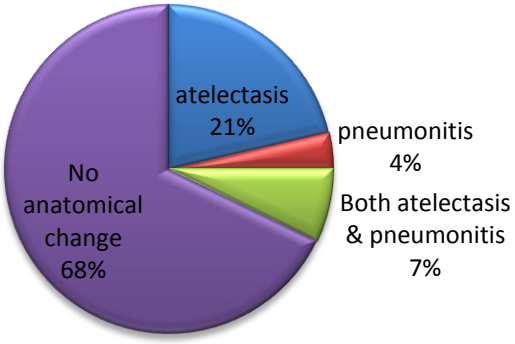

Figure 16. The ratio between atelectasis and pneumonitis change in relation to the patient cohort studied.

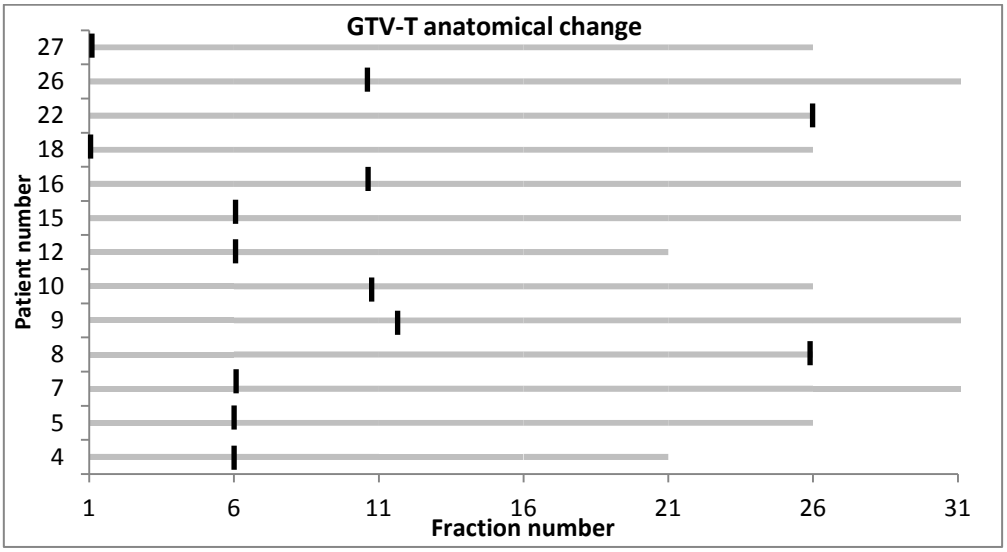

Figure 17. GTV-T anatomical changes. The vertical lines in black represent the fraction when GTV-T anatomical change (tumor shrinkage, growth, deformation and/or displacement) was observed for the remaining patients who were not included in Figure 15. The gray bar represents the start and end time of the performed CBCT.

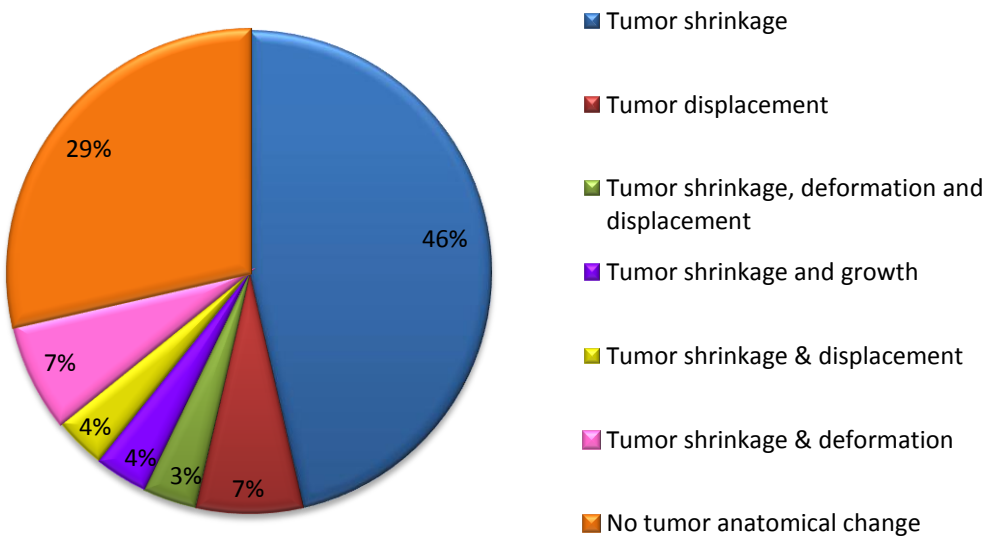

Figure 18. Ratio between tumor anatomical changes for the patient cohort studied.

Significant anatomical change by atelectasis caused mediastinum displacement for patient 25 (Figure 19). This patient was rescanned and replanned as a result of this change. Other significant anatomical changes for some of the adapted patients are presented in Figure 34 – Figure 36 in Appendix II.

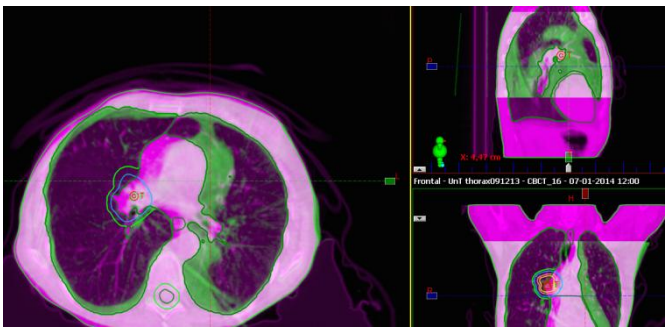

Figure 19. The bone registration of the CBCT at fraction 16 on the initial CT for patient 25 revealed a large anatomical change as a result of appearance of atelectasis to the right of the columna which caused mediastinum displacement (green).

3.4 Discussion

Møller et al.[23] and van Zwienen et al.[21] reported in their articles that the dominant anatomical change seen for lung cancer patients was atelectasis which occurred randomly. Møller presented that out of the 163 patients analyzed 22% showed anatomical changes in form of atelectasis, pneumonitis and/or pleural effusion. It was also presented that 12% of the patients underwent an adaptive strategy with atelectasis as the main reason. Van Zwienen on the other hand reported that out of the 114 patients studied 40% showed tumor regression, 1 % showed tumor progression, 29% showed atelectasis changes in from of dissolving (23%) or increasing

(6%) and 13% showed pleural effusion. Our results show that, out of the 28 analyzed patients there were 9 patients (32%) with anatomical changes, atelectasis and/or pneumonitis. Out of the 9 patients with anatomical changes 67% had atelectasis change (45% appearing, 22% disappearing), 11% pneumonitis (Figure 16) and 22% had both atelectasis and pneumonitis change at the same time. This means that the dominant anatomical change is atelectasis and the changes appeared/disappeared randomly which makes it difficult to predict which time they are likely to appear/disappear during the treatment course. This agrees with both Møller and van Zwienen results. 71% of the patients showed some form of tumor change (tumor shrinkage, growth, deformation and/or displacement). The observed changes occurred most between fraction 6 and 11 (60%). As the anatomical changes occurred randomly it is advisable to perform frequently CBCT during the course of treatment.

Our results for the 8 patients with adaptive strategy showed that atelectasis and tumor change were the reason for adaptation for 5 patients, either alone (38% atelectasis or 25% tumor change), together or as a combination with pneumonitis (Table 8). 40% of the anatomical changes causing adaptation were discovered after fraction 10 with the help of the weekly CBCTs. However, no information was obtained about the actual occurrence of the anatomical changes and the degrees of change between the weekly CBCTs images. It is therefore advisable to perform daily CBCT imaging in order not to miss significant anatomical changes at the time of appearance. For a treatment course of 33 fractions the total dose obtained from daily CBCT would be 0.16 Gy (4.7 mGy[27] x 33 fractions). This is much lower than the total prescribed curative treatment dose which is 60-66 Gy for NSCLC patients and 45Gy for SCLC patients.

4 Conclusions

Soft-tissue match gives more accurate match results despite tumor shrinkage, minimizes GTV-T/IM residual deviation, minimizes the PTV-T margins required and spares healthy tissue irradiation compared to bony match. For semi-automatic soft-tissue match on the primary tumor, match within GTV-T/IM with a 10 or 20 mm margin extension used as match VOIs were most appropriate. For small tumors (< 3 cm^3), match manually on GTV-T/IM itself is advisable. The main bronchi area is a suitable surrogate primarily for centrally positioned mediastinal GTV-N. Symmetric 5.5 mm margins for CTV-T to PTV-T and 5.0 mm margins for medulla-PRV is advisable when soft-tissue match is used. Asymmetric CTV-N to PTV-N margins in the different directions is preferable (9.4 mm in VRT and LNG directions and 6.3 mm in LAT direction).

Anatomical changes occurred randomly with atelectasis as the predominant change. Daily CBCT allows anatomical changes to be observed earlier during the course of treatment, minimizing the risk for missing the changes that can affect the dose distribution or cause the tumor to move outside the treated volume. Observing the significant anatomical changes earlier shorten the time between the observation and the adaptive strategy.

5 Future work

The results of this study showed that more benefits are obtained by using soft-tissue match compared to bony match for lung cancer. Further investigations can therefore be performed to additionally study more aspects that are related to the soft-tissue match. This will give a better understanding for additional benefits and limitations and will help improving the soft-tissue match used. Some of these projects of interest are listed below.

1) Compare DVH for patients with small but significant anatomical changes when bony and soft-tissue match is used to study if soft-tissue match really have less negative dosimetric consequences if no adaptive strategy is performed. This will show if in some cases soft-tissue match can spare the patient the adaptive strategy compared to the bony match. This will be studied by a registration between the first CT and CT-rescan in *Registration* module in *Eclipse* (Varian Medical Systems) TPS and a match (both bony and soft-tissue 3DOF automatic match) between the two scans will be performed. The initial treatment plan for will be copied to the registered rescanned CT image set, and re-calculated using the *Eclipse* TPS (Varian Medical Systems). The same monitor units (MU) and calculation algorithm, Anisotropic Analytical Algorithm (AAA)[35], will be used for both treatment plans. DVH data will be compared between the re-calculated plan and the original plan. This will be done to investigate the dosimetric effects for both the target and healthy tissues if no adaptive strategy is available when anatomical changes relative to the bony and soft-tissue structure are present. The dose constraints for an accepted plan (Appendix I) will be compared to the results of the studied plans.

The reason for not using large anatomic changes when comparing soft-tissue to bony match is because large anatomic changes will affect the patient anatomy in a great extent that will add uncertainties to both the match methods, but small anatomic changes will allow the difference in the result to depend largely on the match method used.

2) Investigate other suitable and stable surrogates for other GTV-N positions and obscured GTV-T. This will help creating a map with different recommended surrogates to use for patients with obscured GVT-T or with only obscured GTV-N as a target. With different possible surrogates the next step would be to evaluate which match strategy is preferable to use, manually match on the surrogate or automatically match on a surrogate plus an extended margin around.

3) Investigate a patient cohort with multiple GTV-Ts and measure the residual GTV-T/IM for the other GTV-T/IMs after a match on one GTV-T/IM. The results will be used to decide the size of the match structure and the confidence level to ensure that 95% of the planned dose is received. The recommended match structure from this study was 2 mm to ensure that 95% of the patients receive 95% of the planned dose. If the results of this investigation shows 95% of the cases have a higher match structure than 2 mm to possible decisions can be made. First decision is to use a match structure which ensures that 95% of the patients receive 95% of the planned dose for the other GTV-T/IMs. Second decision is to have a 2 mm match study for all GTV-T/IMs, but with lower percentage of patients who will receive 95% of the planned dose.

4) Study the reliability of the CBCT to assume that CBCT-scan gives a comparable image with the reference CT. For this study a 4D phantom will be used. 4D CT-scan and a slow CBCT (1.5 min) will be performed using this phantom. The aim is to study the validation of the assumption that a slow CBCT-image is compatible with the Un-tagged 4D-CT-image. In the study one could investigate if there is any systematic differences for different breathing patterns e.g. if the tumor appears smaller/larger on CBCT compared to the CT.

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Appendix I– Dose constraints

NSCLC (NSCLC60, NSCLC66)

2 Gy/ fraction

Priority	DVH constraints	$V_{5\ Gy}$	$V_{20\ Gy}$	$V_{45\ Gy}$	$V_{50\ Gy}$	$V_{55\ Gy}$	$V_{66\ Gy}$	< D >
1	Medulla (α/β=2)			= 0 %				
1	PRV Medulla (α/β=2)				= 0 %			
2	Total lung (α/β=3)	≤ 60 %*	≤ 35 %					≤ 20 Gy
2	Healthy lung (α/β=3)	≤ 40 %						
3	Heart (α/β=3)				≤ 20 %			≤ 46 Gy
3	Esophagus (α/β=3)					≤ 30 %*	= 0 %♦	≤ 34 Gy*

* Aim is to fulfill this criterion

♦ Doses up to 70 Gy can be allowed in small areas (< $1cm^3$)

volume♣	$D_{98\ \%}$	$D_{2\ \%}$	D_{max}
PTV	≥ 95 %	≤ 107 %	≤ 110 %
PTV 60/30	≥ 57 Gy	≤ 64.2 Gy	≤ 66 Gy
PTV 66/33	≥ 62.7 Gy	≤ 70.6 Gy	≤ 72.6 Gy

♣ GTV and CTV should be covered by 95 % iso-dose curve (99 % of the volume). $D_{98\ \%}$ is a starting criterion which is hard to fulfill for most lung patients due to inhomogeneity. Efforts shall be made to reach 95 % iso-dose curve coverage for PTV. This is particularly important in the mediastinum. In free lung tissue a 90% PTV iso-dose curve coverage is accepted. Each case is considered individually. Scroll thorough all slices to make sure there is target dose coverage.

SCLC (SCLC50, SCLC45)

2 Gy/ fraction (1.5 Gy/fraction)ϕ

Priority	DVH constraints	$V_{5\ Gy}$	$V_{20\ Gy}$	$V_{45\ Gy}$	$V_{50\ Gy}$	V_{max}	< D >
1	Medulla (α/β=2)			= 0 %			
1	PRV Medulla (α/β=2)				= 0 %		
2	Total lung (α/β=3)	≤ 60 %*	≤ 35 %				≤ 20 Gy
2	Healthy lung□ (α/β=3)	≤ 40 %					
3	Heart (α/β=3)				≤ 20 %		≤ 46 Gy
3	Esophagus (α/β=3)					= 105 %	≤ 34 Gy*

ϕ N.B. SCLC50 is delivered by 25 fractions, but the risk organs receive less than 2 Gy/fraction. SCLC45 is delivered with 1.5 Gy/fraction, but it is given in 30 fractions. Therefore as starting point same constraints, as the conventional fractioning, is used for both the fractionating schemes.

□ Evaluated individually (depends on the tumor size and position).

* Aim is to fulfill this criterion

volume♣	$D_{98\,\%}$	$D_{2\,\%}$	D_{max}
PTV	≥ 95 %	≤ 107 %	≤ 110 %
PTV 45/30	≥ 42.8 Gy	≤ 48.2 Gy	≤ 49.5 Gy
PTV 50/25	≥ 47.5 Gy	≤ 53.5 Gy	≤ 55 Gy

♣ GTV and CTV should be covered by 95 % iso-dose curve (99 % of the volume). $D_{98\,\%}$ is a starting criterion which is hard to fulfill for most lung patients due to inhomogeneity. Efforts shall be made to reach 95 % iso-dose curve coverage for PTV. This is particularly important in the mediastinum. In free lung tissue a 90% PTV iso-dose curve coverage is accepted. Each case is considered individually. Scroll thorough all slices to make sure there is target dose coverage.

Appendix II – Figures and tables

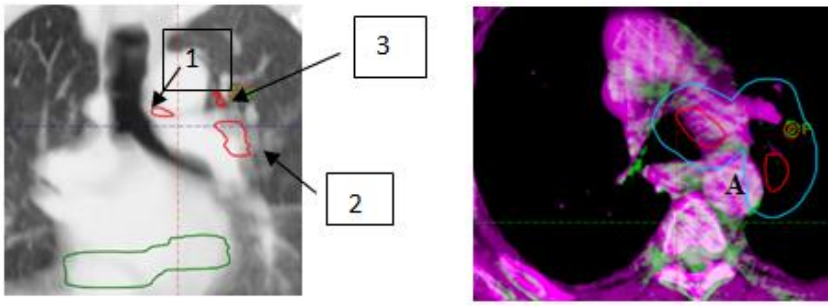


Figure 20. Left: GTV-N locations for patient 7 (frontal plane). Right: **A** is descending aorta (transverse plane) which is a surrogate used for GTV-N2 and GTV-N3 in the left image.

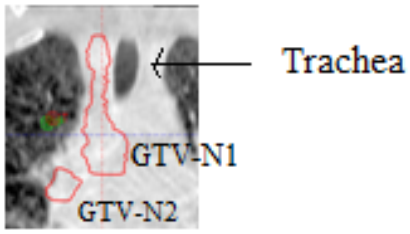


Figure 21. GTV-N1 & 2 for patient 12 (frontal view). Trachea is used as a surrogate for GTV-N1.

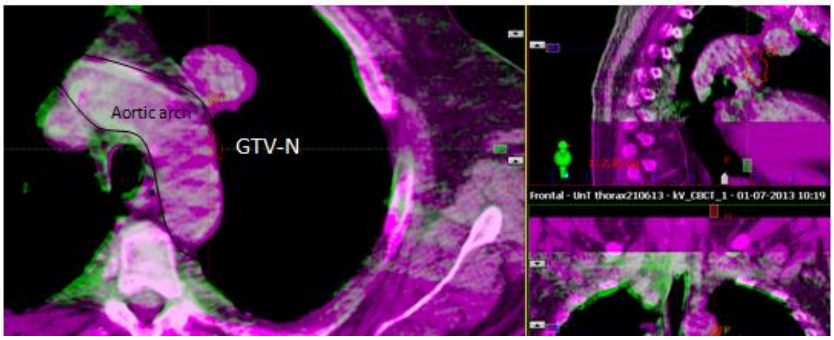


Figure 22. GTV-N and Aortic arch as a surrogate for GTV-N for patient 15 (all planes).

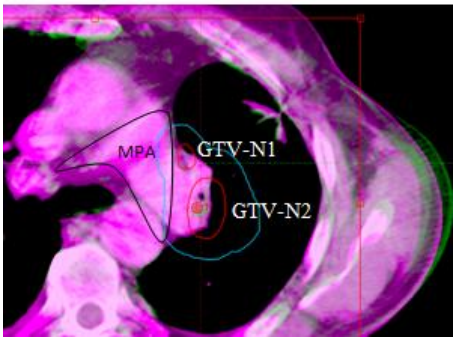


Figure 23. GTV-N1 & 2 for patient 22. Main pulmonary artery, MPA, as a surrogate for both GTV-Ns (transverse view).

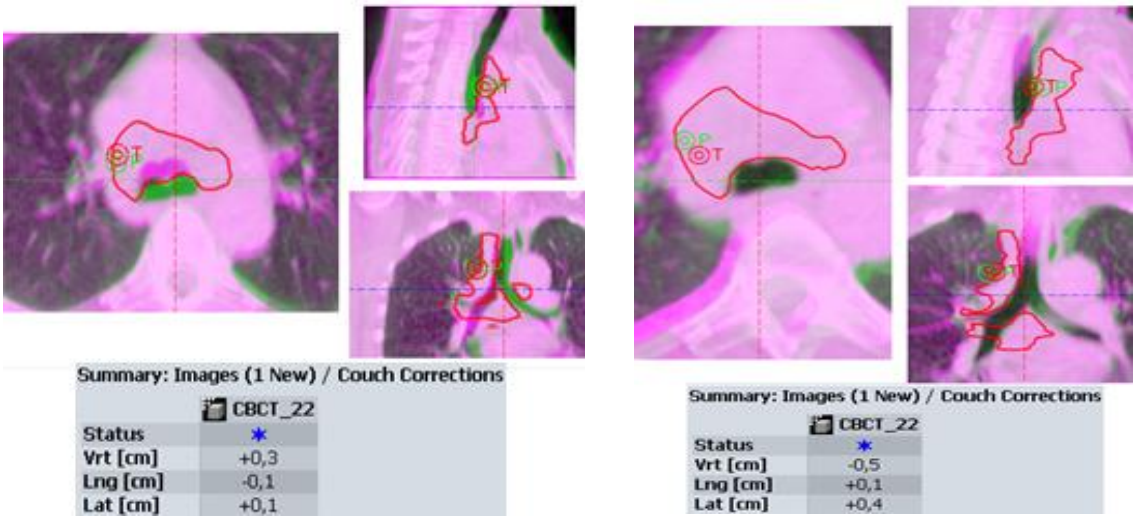


Figure 24. Left: Bronchi (GTV-N surrogate (red)) residual deviation after soft-tissue GTV-T/IM+5mm match, Patient 19, fraction 22. Right: Manually corrected deviation for bronchi. The difference in translational shifts between the manual and automatic soft-tissue match gives the GTV-N residual set-up deviation, VRT-deviation: -0.5 - (0.3) = -0.8 cm, LNG-deviation: 0.1 - (-0.1) = 0.2 cm and LAT-deviation: 0.4 – (0.1) = 0.3 cm.

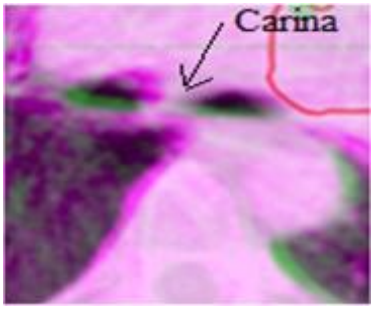


Figure 25. Carina (between right and left bronchus) as a surrogate for GTV-T/IM (transverse view) for patient 1.

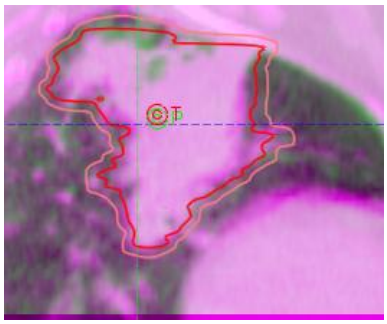


Figure 26.GTV-T/IM (red) residual deviation, 3 mm (orange) after soft-tissue GTV-T/IM+10 mm automatic match for patient 5 (sagittal plane). The deviation is due to both set-up deviation and little tumor growth.

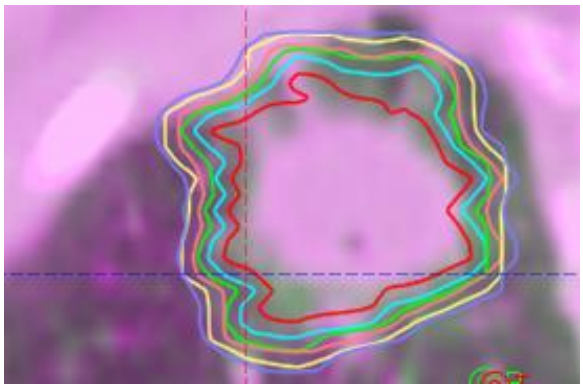


Figure 27. Shows delineated deviations (1-5 mm) around GTV-T/IM (red) for patient 19. GTV-T/IM residual deviation is 2 mm (green) after soft-tissue GTV-T/IM+2 mm automatic match (Frontal view).

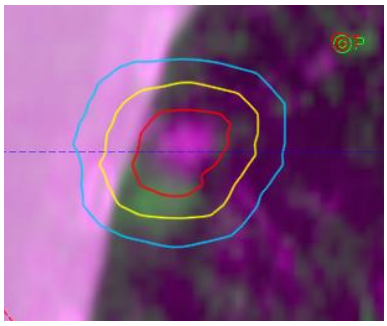


Figure 28. 8 mm GTV-T/IM (red) residual deviation after bony match for patient 10, fraction 26.GTV-T/IM in Reference CT (pink). GTV-T/IM in CBCT (green) (Frontal view). Match structure (yellow) and PTV-T (blue). When soft-tissue match was performed the residual GTV-T/IM deviation was 1 mm. Match structure is a defined extra structure at Herlev Hospital to account for the fact that CTV-T is not seen, and it is assumed that if GTV-T lies inside the match structure, CTV-T lies inside PTV-T.

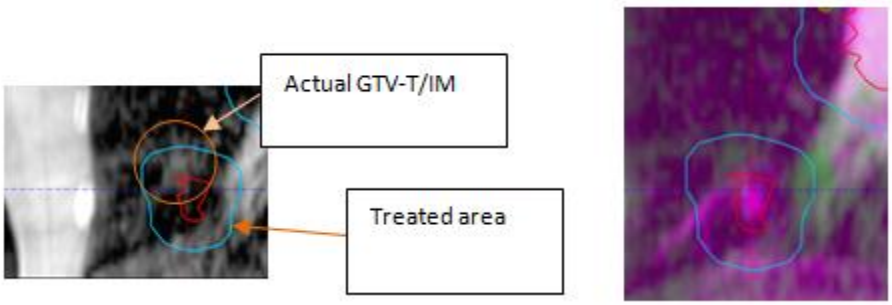


Figure 29. Left: actual GTV-T/IM position in fraction 1 for patient 18 after bony match. It can be seen that part of the GTV-T/IM is outside the treated area. Right: colored deviation of left image (frontal view). The large deviation in GTV-T/IM was seen for all CBCT for this patient when bony match was performed. This means that anatomical change in GTV-T/IM (tumor displacement) occurred and a rescan should been performed.

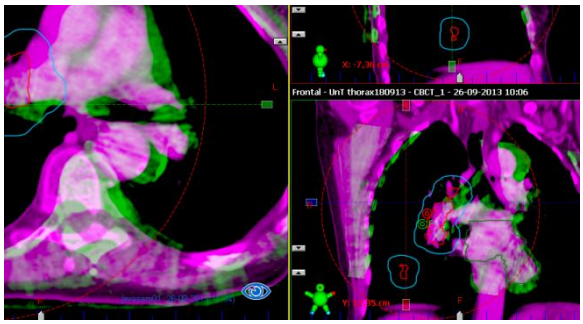


Figure 30. Medulla and mediastinum deviation for patient 18, fraction 1, after soft-tissue GTV-T/IM+5mm match. Large deviation in bone was also seen for patient 10 when soft-tissue match was performed instead of bony match (Figure 28).

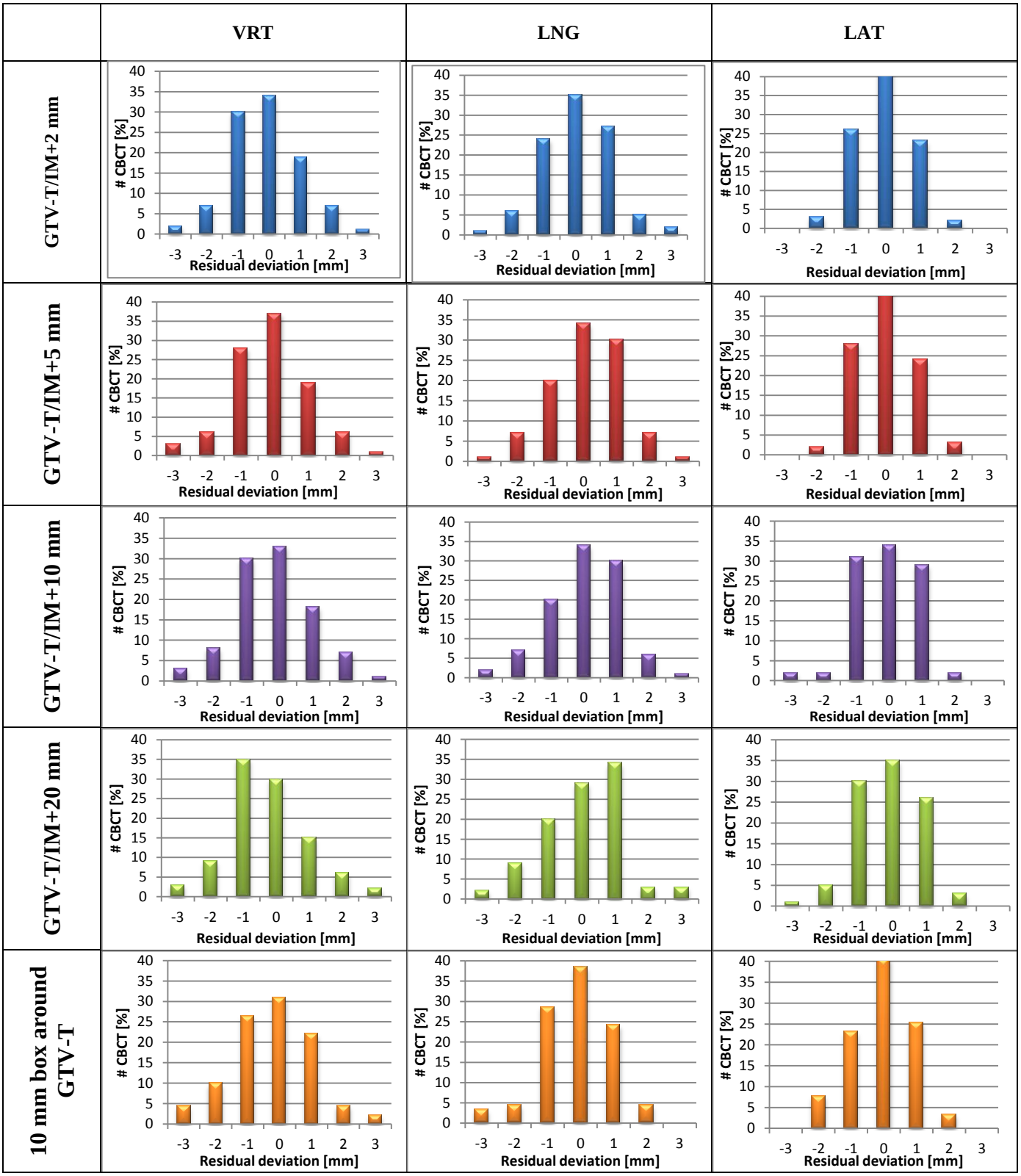


Figure 31. GTV-T/IM residual deviation after soft-tissue match (utilizing GTV-T/IM plus a 2, 5, 10 and 20 mm symmetrical margin, and square VOI enclosing the GTV-T with a 10 mm symmetrical margin).

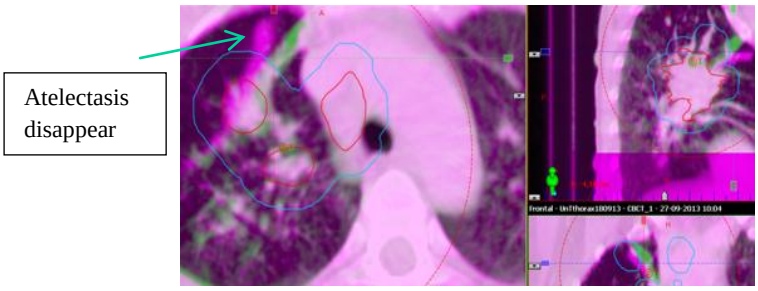


Figure 32. Atelectasis disappear (pink) close to GTV-T. patient 14, fraction 1.

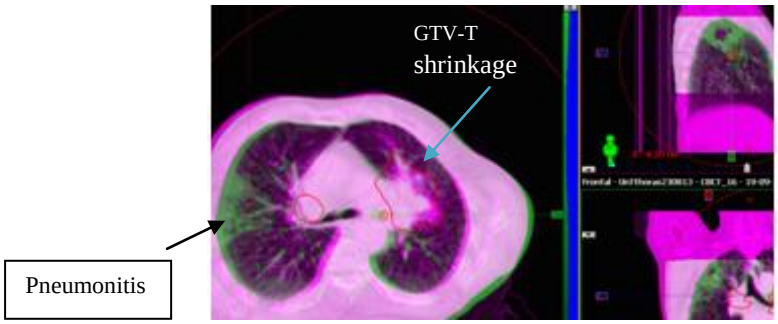


Figure 33. Pneumonitis and tumor shrinkage (patient 11, fraction 11).

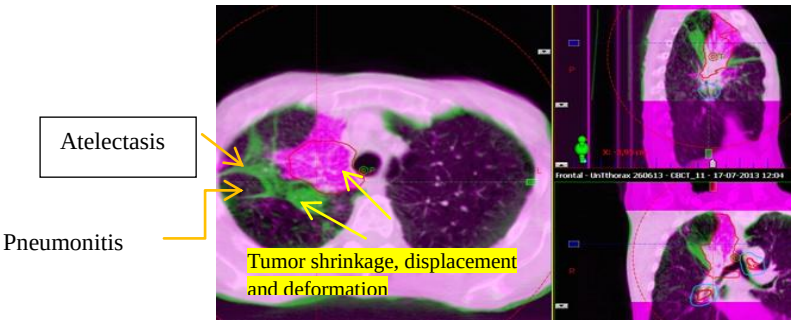


Figure 34. The bone registration of the CBCT at fraction 11 on the initial CT for patient 2 revealed a large anatomical change caused by atelectasis , pneumonitis and tumor shrinkage, displacement and deformation as a result of loosening from the thoractic wall

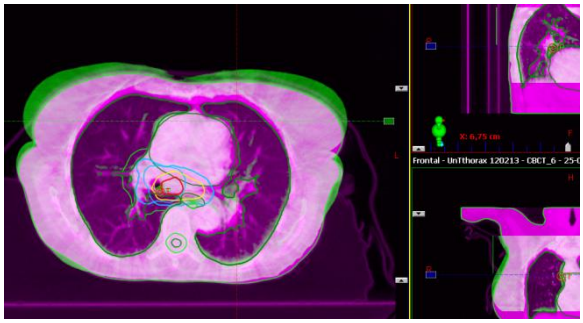


Figure 35. The bone registration of the CBCT at fraction 6 on the initial CT for patient 24 revealed significant anatomical change as a result of bloated breasts.

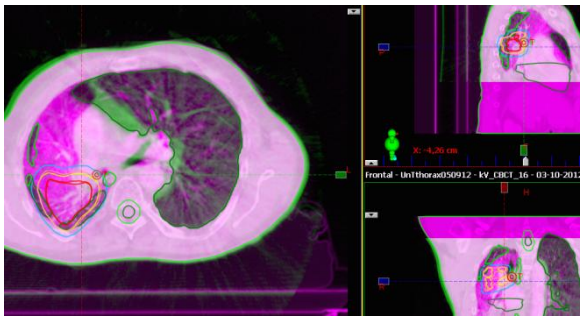


Figure 36. The bone registration of the CBCT at fraction 11 on the initial CT for patient 28 revealed a large anatomical change as a result of atelectasis disappear and tumor shrinkage.

Appendix III – Calculated systematic and random set-up errors

Table 9. Systematic set-up error,Σ, and random set-up error, σ, based on population measurements to calculate medulla-PRV margins for all soft-tissue match methods.

		Σ [mm]	σ [mm]	Σ [mm]	σ [mm]	Σ [mm]	σ [mm]	Σ [mm]	σ [mm]
Match method		**VRT [mm]**		**LNG [mm]**		**LAT [mm]**		**3D [mm]**	
	Soft-tissue: GTV-T/IM+2mm	1.67	1.68	1.63	1.95	1.54	1.33	1.34	1.74
	Soft-tissue: GTV-T/IM+5mm	1.48	1.60	1.72	2.13	1.47	1.39	1.25	1.69
	Soft-tissue: GTV-T/IM+10mm	1.58	1.52	1.64	2.11	1.35	1.28	1.29	1.69
	Soft-tissue: GTV-T/IM+20mm	1.38	1.22	1.64	1.97	1.19	1.22	1.14	1.36
	Soft-tissue: 1 cm box around GTV-T	1.35	1.32	1.55	2.24	1.21	1.18	1.26	1.50

Table 10. Systematic set-up error,Σ, and random set-up error, σ, based on population measurements to calculate CTV-T to PTV-T margins for all the match methods.

		Σ [mm]	σ [mm]	Σ [mm]	σ [mm]	Σ [mm]	σ [mm]	Σ [mm]	σ [mm]
Match method		**VRT [mm]**		**LNG [mm]**		**LAT [mm]**		**3D [mm]**	
	Soft-tissue: GTV-T/IM+2mm	0.521	1.07	0.702	0.968	0.546	0.744	0.662	0.979
	Soft-tissue: GTV-T/IM+5mm	0.522	1.08	0.782	0.906	0.542	0.735	0.570	0.949
	Soft-tissue: GTV-T/IM+10mm	0.598	1.08	0.788	0.911	0.561	0.766	0.618	0.978
	Soft-tissue: GTV-T/IM+20mm	0.567	1.11	0.677	1.22	0.541	0.898	0.595	1.07
	Soft-tissue: 1 cm box around GTV-T	0.639	1.11	0.680	1.04	0.540	0.891	0.580	1.02
	Bone: Medulla-PRV+2.5 cm	1.46	2.02	1.67	2.28	1.33	1.54	1.19	2.04

Table 11. Systematic set-up error,Σ, and random set-up error, σ, based on population measurements to calculate CTV-N to PTV-N margins for all the match methods.

		Σ [mm]	σ [mm]	Σ [mm]	σ [mm]	Σ [mm]	σ [mm]	Σ [mm]	σ [mm]
Match method		**VRT [mm]**		**LNG [mm]**		**LAT [mm]**		**3D [mm]**	
	Soft-tissue: GTV-T/IM+2mm	2.24	1.76	1.84	2.13	1.26	1.29	1.68	1.54
	Soft-tissue: GTV-T/IM+5mm	2.15	1.70	1.94	2.15	1.13	1.22	1.77	1.46
	Soft-tissue: GTV-T/IM+10mm	2.18	1.61	1.97	2.15	0.946	1.21	1.74	1.54
	Soft-tissue: GTV-T/IM+20mm	1.99	1.57	1.97	2.05	0.830	1.22	1.62	1.55
	Soft-tissue: 1 cm box around GTV-T	2.18	1.54	1.92	2.23	1.03	1.19	1.70	1.53
	Bone: Medulla-PRV+2.5 cm	1.40	1.52	1.63	2.58	1.23	1.28	1.29	2.08

Appendix IV – Statistical analyses

Statistical analysis to study the difference in residual GTV-T/IM (obtained as described in 2.3.4, **III**) between the five soft-tissue match methods was performed using one-way ANOVA and multiple comparisons test. The analysis was performed just for the 3DOF match.

Statistical analysis showed no significance different in mean residual deviation for GTV-T/IM between the 5 soft-tissue match methods. Box plots of the GTV-T/IM residual set-up deviation for the five soft-tissue match methods are illustrated in Figure 37.

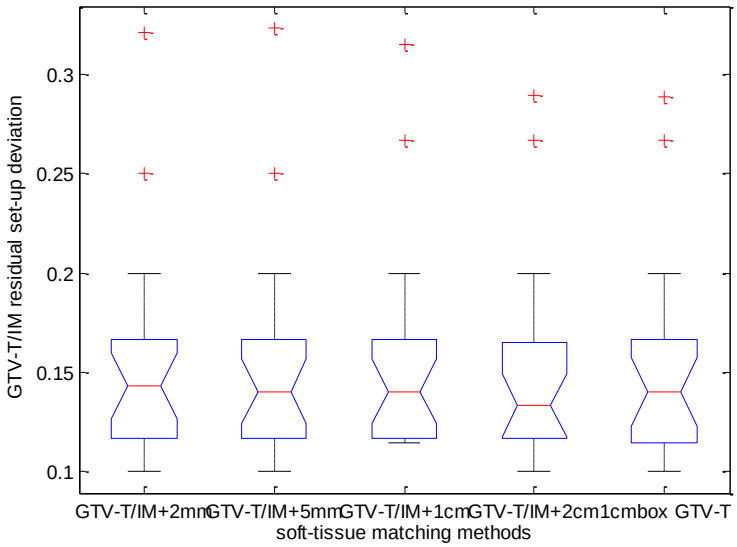


Figure 37. Box plots with GTV-T/IM residual deviation for the different soft-tissue match methods. The box boundaries represent the 25th and 75th percentiles, respectively. The horizontal lines represent medians. Whiskers mark the highest and lowest values of the data set that are within 1.5 times the inter quartile range of the box edges (the fence). The plus signs mark individual values outside the range of the whiskers. The notches show median confidence interval. Notches give a rough guide to significance of medians' difference; there is evidence of a statically significant difference (with 95 % confidence) between two groups if the notches of their boxes do not overlap. Note that both ANOVA1 and multiple comparisons test which was used compare the difference in mean, not in median.

The calculated PTV-N margins for all the soft-tissue match methods shows that different margin values obtained in all the different directions (Table 6). Clinical it is worth knowing if there is actually significance difference between GTV-N margins in the three directions to know if a symmetric or an asymmetric margin is to be delineated around CTV-N. Significance analysis was performed to study if there was significance difference in VRT, LNG and LAT GTV-N deviations for the five soft-tissue match methods. A distribution histogram for GTV-N residual deviations in all directions plotted in Figure 11, for soft-tissue GTV-T/IM+20 mm match method shows that mean value in GTV-N deviation is close to 0 for all directions. This means a significance analysis test such as ANOVA can't be used because there will not be a difference in mean deviation in the three directions. Instead F-test was used to study the variance of the three directions. First a *multiple-sample F-test* was performed to study if there is a significance difference in variance between the three directions (with 5 % significance level). If the multiple-test shows significance, a further *two-sample F-test* (with 5 % significance level) was performed to study which two directions had a significance difference in variance (Table 12).

Table 12. Statistical significance analysis (multiple-sample F-test and two-sample F-test) results for variance of GTV-N residual set-up deviation in all three directions. Analysis performed for all soft-tissue match methods.

Soft-tissue match method	Multiple-sample F-tests for equal variances (*p*-value)	Two-sample F-test
GTV-T/IM+ 2 mm margin	$p = 0.003$	Significant variance difference between VRT and LAT GTV-N deviation
GTV-T/IM+ 5 mm margin	$p = 0.002$	Significant variance difference between LNG and LAT, and significance variance difference between VRT and LAT GTV-N deviation
GTV-T/IM+ 10 mm margin	$p = 0.0001$	Significant variance difference between LNG and LAT, and significance variance difference between VRT and LAT GTV-N deviation
GTV-T/IM+ 20 mm margin	$p = 0.0001$	Significant variance difference between LNG and LAT, and significance variance difference between VRT and LAT GTV-N deviation
10 mm box around GTV-T	$p = 0.007$	Significant variance difference between LNG and LAT, and significance variance difference between VRT and LAT GTV-N deviation

It is clear from Table 12 that there is no significance difference in GTV-N deviation in VRT and LNG directions. But both VRT and LNG GVT-N deviation variances differ from LAT GTV-N deviation variance for all the soft-tissue match methods except for GTV-T/IM+2 mm match method. (For GTV-T/IM+2mm match method the significance variance difference is just between VRT and LAT GTV-N deviation).

An analysis was also performed to study if there was significance difference in mean 3D GTV-N deviation between the five soft-tissue match methods. Both ANOVA1 ($p = 0.97$) and multiple comparisons shows no significance different.

For GTV-T/IM residual deviations measured as described in section 2.3.4, **IV**, the deviations was measured in all three directions (VRT, LNG and LAT). Distribution histograms for GTV-T/IM residual deviations in all directions for all the soft-tissue match methods are demonstrated in Appendix II, Figure 31. PTV-T margins calculated in the three directions shows that the margins are close to each other in all directions (Table 5). The mean deviations in all directions are close to zero. Significance analyses used is therefore F-tests the same way as for GTV-N deviation described above (Table 13).

Table 13. Statistical significance analysis (multiple-sample F-test and two-sample F-test) results for variance of GTV-T/IM residual set-up deviation in all three directions. Analysis performed for all soft-tissue match methods.

Soft-tissue match method	Multiple-sample F-tests for equal variances (*p*-value)
GTV-T/IM+ 2 mm margin	$p = 0.4$
GTV-T/IM+ 5 mm margin	$p = 0.2$
GTV-T/IM+ 10 mm margin	$p = 0.3$
GTV-T/IM+ 20 mm margin	$p = 0.6$
10 mm box around GTV-T	$p = 0.7$

Results in Table 13 show no significance difference in GTV-T/IM deviation variance between the three directions.

Appendix V – Clinical implementation protocol

Online 3DOF soft-tissue match steps:

[1] Perform CBCT-scan

[2] Auto match on accelerator

Auto match is performed for partly or whole visible GTV-T/IM. It is performed by clicking on *"Auto Match Images"* or by clicking on *Match Images"* then select *"Auto anatomy match"* in the roller curtain menu to the right, Figure 38.

Press *"Stop"* when the auto match is selected and ensure that the match parameters follow the points [3] below.

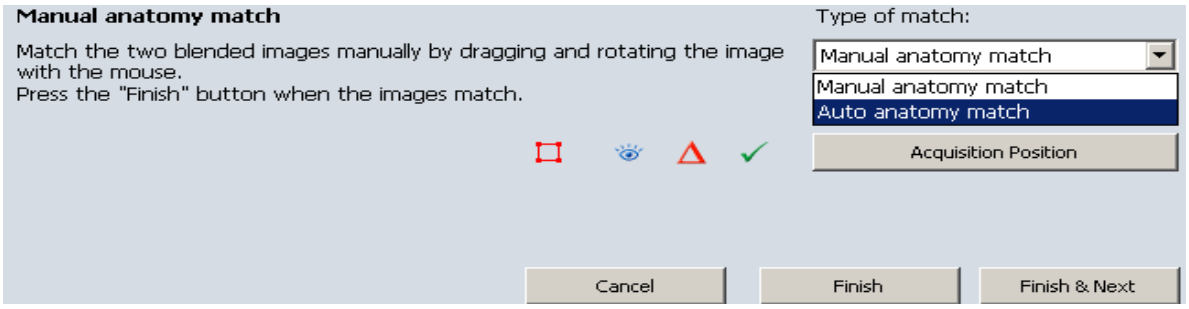


Figure 38. Choose *"Auto anatomy match"*, by first clicking on *"Manual anatomy match"* icon.

[3] Set-up before auto match is performed

Auto match is performed on GTV-T/IM with a 1.0 cm margin. 3DOF match is used (VRT, LNG and LAT).

- Place the match ROI (red box) so it covers the defined VOI used for the match (GTV-T/IM + 10 mm) in all planes: transverse, sagittal and frontal plane, Figure 39.

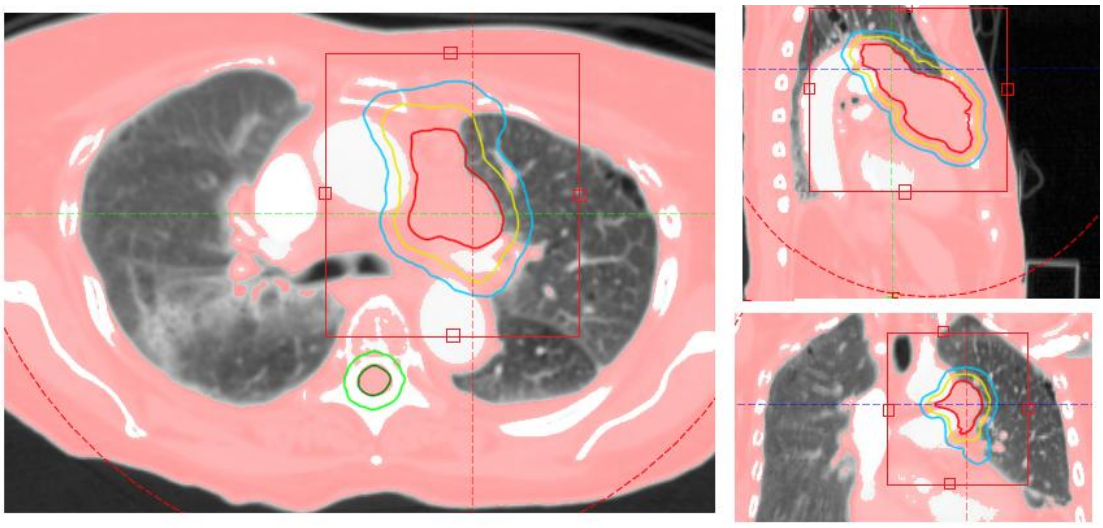


Figure 39. The pixels used for soft-tissue match are colored with red/pink and are placed within the defined volume of GTV-T/IM + 1.0 cm. the colored pixels have an intensity between -150 and 150 HU. Observe that the match ROI is placed within around the defined VOI used for the match (GTV-T/IM + 10 mm).

- Fill in the match parameters for auto match according to the list below and Figure 40.

- Parameter Set: Select: *"Thorax 3D"*
- Axes: Select: *"LAT", "LNG", "VRT"*
  Select: *"Intensity Range"*
  Select: "*Structure VOI*"

- Intensity Range: Fill in: HU-values:
  - *From: **-150** to **150***
  Uncheck:
  "last step only"

- Structure VOI: Select: *"GTV-T/IM"* (it is marked which GTV-T/IM to use if there are more than GTV-T/IM)
  Select: *"margin"*
  Fill in: *"margin size"* into:
  ***1.0** cm*
  Uncheck:
  - *"last step only"*

- Press on *"Start"*. Auto match is performed.

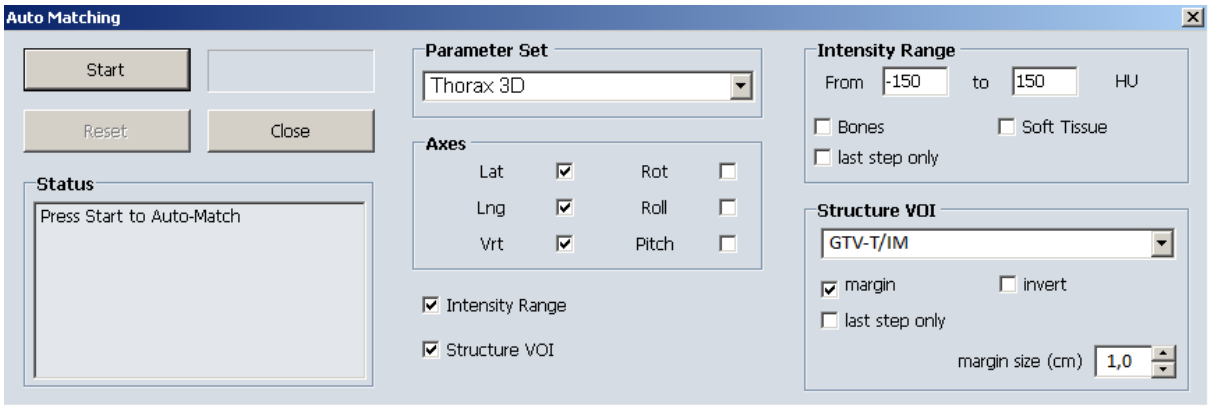


Figure 40. Match parameters for auto soft-tissue match.

Verification of tumor position online for CBCT match (RTT):

- Lung Tumor on CBCT scan is visualized best by right-clicking in both the right and left "*window-level*" axis, select "*Range*" and select "*Lung*" (both right and lest axis should have the same range to be able to compare them, left: reference CT, right: CBCT), then drag the window-level slightly upward / downward to obtain a good image quality of the tumor (Figure 41). If the window-level is not enabled, it can be activated by click on "*Window / Level*" .

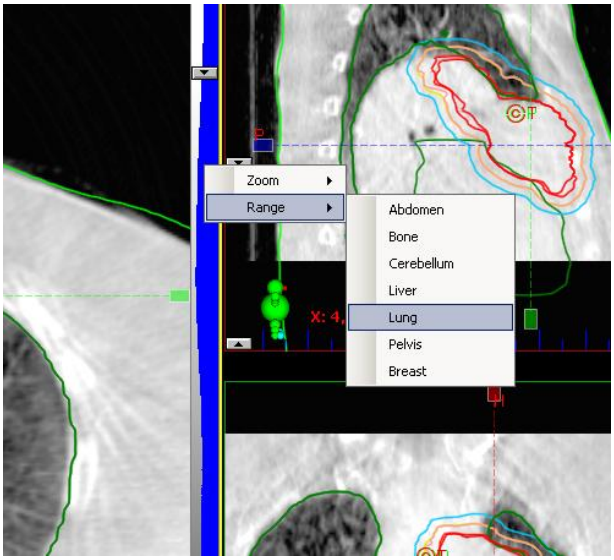


Figure 41. Choice of "*window-level*" for best visualization of lung tumor in CBCT.

- Turn of all structures by pressing on *"Show/hide structures"* .
- Relevent match structure for the tumor, GTV-T/IM, PTV-(T+N) avd medulla-PRV should be activated.
- The structures is activated by pressing on **Plan Tree** to the left of the screen, then mark the desired structures in the list, Figure 42.

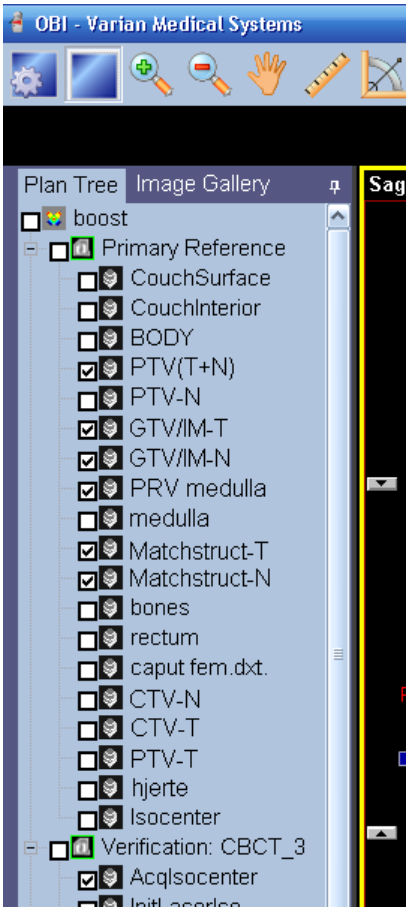


Figure 42. Activation of relevant structures.

- Use different colors on CBCT and reference CT by activating the "*color blending*", by click the "*Toggle On / Off Color Blending*" . You can also use the "*split window*" . Alternatively, you can "*blend*" between therapy scan and CBCT, and keep an eye on GTV-T/IM.
- If the automatic match still doesn't fit between the reference CT and CBCT, manual match can be used by clicking on "*Match Images"* and the image is moved into position using the arrow keys.
- Important to focus on when verification the soft-tissue (Figure 43):

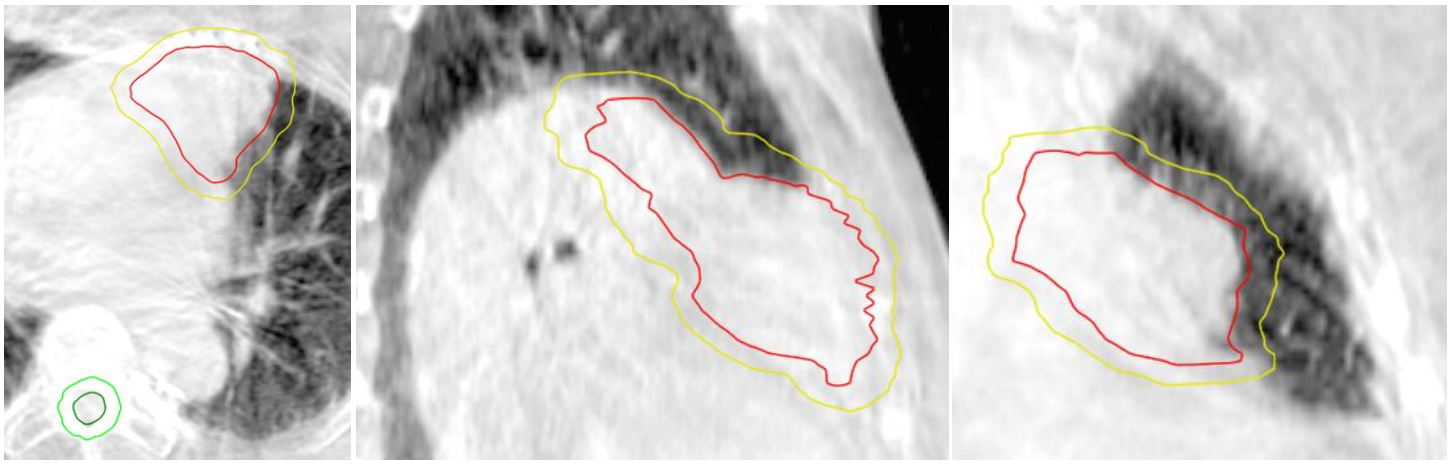
Verification that GTV-T/IM lies within the match structure (delineated in yellow in the reference CT, Figure 42, is performed by RTT.

- Assessed that there is congruence in the area with the tumor/atelectasis in reference CT and CBCT.
- Make sure that the GTV-T/IM (all GTV-T/IM if there are more than one) seen in the CBCT lies within 2 mm the match structure (colored yellow). This ensures that the target lies the irradiated PTV volume with the prescribed dose.

Match structure includes the margins that account for internal motion and volume change (internal margin – IM), and set-up uncertainties (set-up margin – SM). Match structure is delineated around both the primary tumor and malignant lymph nodes. Make also sure that the surrogate used for GTV-N lies within the delineated surrogate in the reference CT.

- Make sure that the spinal cord lies within the 5 mm delineated "*medullaPRV*" structure (colored in light green). Using abdomen window-level (for both the reference CT and CBCT) make it easier to visualize the spinal cord.

- The assessment is performed by scrolling through all the three planes (transverse, sagittal and frontal) within the match structure (colored yellow) for GTV-T/IM and GTV-N verification. For the spinal cord scroll through the whole irradiated volume (PTV-(T+N)) in all the three planes.
- If an manual match was performed and:
  (a) Spinal cord outside the "*medullaPRV*" in transverse plane as a result of e.g. rotation or lower/higher arm: The patients should be repositioned and a new CBCT is performed again. If the spinal cord still outside "*medullaPRV*" after the new CBCT: Contact a physician/oncologist.
  (b) GTV-T/IM outside the match structure, but inside PTV-T: Perform the treatment but inform the physician about it. If GTV-T/IM still outside the match structure three times in a row: Contact a physician/oncologist before performing the treatment. The physician and the oncologist decide if an adaptive strategy is to be performed.
  (c) GTV-T/IM outside both the match structure and PTV-T: Don't perform the treatment and contact a physician/oncologist.
- If there are problems in performing the match contact a physician.
- If there are anatomical changes observed (atelectasis, pneumonitis, pleural effusion and/or large tumor change) contact an oncologist and/or a physician before performing the treatment.
- It is **zero tolerance** and "Apply shift" which are performed before running the treatment.



Transverse **Sagittal** **Frontal**

Figure 43. Verification of correct tumor match using lung window-level.

Manual soft-tissue match for special cases

For small tumors it is recommended to match manually on GTV-T/IM since the automatic match is not stable.

- Follow the same steps as the automatic match except for step [2] where the following should be performed instead:
  - Manual match is performed by clicking on *"Match Images"* then select "*Manual anatomy match"* in the roller curtain menu to the right, Figure 38. Move the image into position using the arrow keys.

Appendix VI – Abstract accepted at the 2014 "8th European Conference on Medical Physics"

Title: 'Soft-tissue matching methods for lung cancer radiotherapy - benefits, limitations and margin determination'

Background: The purpose of this study was to evaluate five different CBCT semi-automatic soft-tissue match methods for lung cancer patients and to calculate the corresponding CTV to PTV margins, both for primary tumor and lymph nodes.

Material and methods: For 23 lung cancer patients (16 NSCLC, 7 SCLC) treated with radiotherapy, 135 weekly CBCT set-up images were retrospectively matched to the planning CTs by five different match methods using the registration software Offline Review, version 10.0 (Varian Medical Systems). Four match methods utilized the volume of interest (VOI) of the 4DCT defined GTV, including the internal motion (GTV-T/IM), plus a 2, 5, 10 or 20 mm symmetrical margin, respectively. The fifth match method used a square VOI enclosing the GTV-T with a 10 mm symmetrical margin. An intensity range of [-150;150] HU was used for automatic soft-tissue matches. Residual GTV-T/IM set-up deviations in all directions were studied for each match and PTV-T margins were calculated. Additionally, stable surrogates close to GTV-N was used for the residual GTV-N set-up deviation measurements and PTV-N margin calculations.

Results: All match methods gave similar residual GTV-T/IM set-up deviations, ranging between [0;3] mm (62 % within 0-1 mm, 34 % within 1-2 mm, and 4% within 2-3 mm), resulting in [5.2;5.8] mm PTV-T margins. Match methods utilizing larger VOIs were more stable compared to match methods using smaller VOIs. Auto match on small targets (< 3 cm^3) was problematic, and not possible for match method 5. For 77 % of the patients with lymph nodes, the main bronchi area was a suitable stable surrogate. For the remaining lateral GVT-Ns the aortic arch and the main pulmonary artery were suitable as surrogates. Residual GTV-N set-up deviations ranged between [-8;10] mm resulting in PTV-N margins between [6;9.8] mm.

Discussion: For semi-automatic soft-tissue match on the primary tumor, match within GTV-T/IM with a 10 or 20 mm margin extension used as matching VOIs were most appropriate. For small tumors (< 3 cm^3), matching manually on GTV-T/IM itself is advisable. The main bronchi area is a suitable surrogate primarily for centrally positioned mediastinal GTV-N.