Differences in Radiotherapy Delivery and Outcome Due to Contouring Variation

Gross tumor volume (GTV) delineation is central for radiotherapy planning. It provides the basis of the clinical target volume and, ultimately, the planning target volume which is used for dose optimization. Manual GTV delineations are prone to intra- and inter-observer variation and automatic segmentation methods also produce different results. There is no consensus on how to account for the contouring uncertainty, but has been suggested to incorporate it into the planning target volume (PTV) margin. Current recipes for the PTV margin are based on normal distribution assumptions and are more suitable for setup and execution errors. In this study we use the GTV delineations made by 6 experienced clinicians to create delineation-specific dose plans. These dose plans are then used to calculate theoretic tumor control probabilities (TCP) differences between delineations. The results show that current margin recipes are inadequate for maintaining the same TCP despite manual delineation variation. New methods to account for delineation variation should be developed.
Analysis of Target Volume Definition Using CT, MRI and FDG-PET in Radiotherapy Treatment Planning of Anal Cancer

Purpose/Objective: The main objectives were to explore the intermodality and intra-observer variations of anal cancer GTV delineations on CT, MRI and PET images.

Materials and Methods: 22 patients with biopsy-proven anal carcinoma scheduled for curative RT underwent FDG-PET/contrast enhanced CT and MRI. The delineations of GTV were done twice for each imaging modality with a minimum of 3 months in between. Delineations on the CT and MRI were done by routine methods. For the PET part three different cut-off values were used: SUV 2.5, 40% and 50% of maximum SUV, respectively. The GTVs were compared for: size, volume changes, center-of-mass (COM) and non-overlapping regions, regarding inter-modality and intra-observer variations. Wilcoxon rank sum test and ANOVA analysis were used, where p < 0.05 was considered significant.

Results: 1. Volume size: The mean GTV-CT of the 1st and 2nd delineation was significantly larger compared to the mean GTV-MRI and the median GTVs from the different PET cut-offs (33.9 cm3, 18.0 cm3, 15.6 cm3, 14.8 cm3 and 10.3 cm3, respectively). The intraobserver differences in volume size were small and non-significant. It was additionally found that the mean GTV-CT increased when overlaying either mean GTV-MRI or one of the three mean GTV-PETs (17%, 24%, 56% and 36 %, respectively). 2. COM: The inter-modality differences in COM were found to be > 1cm between CT-MRI, CT-PET2.5 and MRI-PET2.5. However, the intraobserver differences in COM were found to be minor. 3. Non-overlap: There were significant differences in mean of the non-overlapping regions using the CT or MRI (20.5% and 22.5%) compared to the different PET cut-offs (5.5%, 6.4% and 5.8%), respectively.

Conclusions: Delineations of anal tumors are difficult. GTV-CT was the largest compared to GTV-MRI and the different GTV-PETs. Although the GTV-CT were larger, it did not always cover the GTVs of MRI and PET. The GTV-CT increased if overlaying GTV-MRI or one of the GTV-PETs. Based on our study, our recommendations are not to use CT solely for delineating anal tumors; MRI or PET should be considered as a second imaging modality.

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Does the Progress in Radiation Therapy Make Higher Demand to Interobserver Variability Correction? A Case Study of IMRT and Volumetric Arc Therapy

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Authors: Hollensen, C. (Intern), Persson, G. (Ekstern), Højgaard, L. (Ekstern), Specht, L. (Forskerdatabase), Larsen, R. (Intern)
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Scopus rating (2015): SJR 2.333 SNIP 1.756 CiteScore 3.83
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Purpose/Objective: Gross tumour volume (GTV) delineation is central for radiotherapy planning. It provides the basis of the clinical target volume and finally the planning target volume (PTV) which is used for dose optimization. GTV delineations are prone to intermethod and interobserver variation. In clinical studies this variation is commonly represented by geometrical volume comparison measures (GVCMs) as volume assessment, centre of mass and overlap. The correlation between these measures and the radiotherapy plan are however unclear. The aim of the present study is to investigate the correlation between GVCMs and the radiotherapy plans of patients with peripheral lung tumours.

Materials and Methods: Peripheral lung tumours of 10 patients referred for stereotactic body radiotherapy in 2008 were delineated by 3 radiologists and 3 oncologists. From these GTV delineations 6 different radiotherapy plans with RapidArc© were created for each patient using the same procedure for creation of PTV and dose optimisation. For each patient the volume receiving 90 % of the prescribed dose (V90) and the minimum dose that 90 % of the volume receives (D90) was extracted for the 6 delineations on each of radiotherapy plans. GVCMs as Dice overlap coefficient, mismatch, volume difference, center of mass distance, and Haussdorff distance were extracted between each pair of the delineations of GTV for each patient. Mismatch was defined as the volume of a GTV delineation outside the GTV delineation used to create the PTV divided volume of the GTV used to create the PTV. The Pearson correlation between the GVCMs and their corresponding difference in V90 and D90 was calculated and their statistical difference from zero and each other was tested with a ttest with a pvalue of 0.05.

Results: The V90 and D90 were extracted for the 6 different PTVs on the 60 radiotherapy plans. The standard deviation for V90 and D90 were 5.5 % of the volume and 4.1 Gy respectively, The standard deviation in one image plane of one patient can be seen in the figure.
Figure: Standard deviation of the different radiotherapy plans in one plane for one patient. GTV contours in white. 150 estimations of the difference between the volumes were calculated for each of the GVCMs. The correlation results can be seen in the table.

Table: Correlation coefficients

<table>
<thead>
<tr>
<th></th>
<th>Correlation of V90</th>
<th>Correlation of D90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dice Coefficient</td>
<td>0.44 ± 0.10</td>
<td>0.43 ± 0.10</td>
</tr>
<tr>
<td>Mismatch</td>
<td>0.82 ± 0.03</td>
<td>0.71 ± 0.05</td>
</tr>
<tr>
<td>Volume difference</td>
<td>0.37 ± 0.10</td>
<td>0.32 ± 0.10</td>
</tr>
<tr>
<td>Center of mass distance</td>
<td>0.37 ± 0.09</td>
<td>0.49 ± 0.08</td>
</tr>
<tr>
<td>Hausdorff distance</td>
<td>0.37 ± 0.10</td>
<td>0.37 ± 0.10</td>
</tr>
</tbody>
</table>

All the correlation coefficients were found significantly different from 0. The correlation coefficient for mismatch was significantly different from all the other GVCMs for both V90 and D90. The correlation coefficient for center of mass was significantly different from the volume difference for D90.

Conclusions: Mismatch between GTVs is significantly more correlated with V90 and D90 than other GVCMs. Mismatch between GTVs could be used as an indicator for difference in V90 and D90 of their corresponding radiotherapy plans.
Interobserver delineation variation in lung tumour stereotactic body radiotherapy

Objectives
In radiotherapy, delineation uncertainties are important as they contribute to systematic errors and can lead to geographical miss of the target. For margin computation, standard deviations (SDs) of all uncertainties must be included as SDs. The aim of this study was to quantify the interobserver delineation variation for stereotactic body radiotherapy (SBRT) of peripheral lung tumours using a cross-sectional study design.

Methods
22 consecutive patients with 26 tumours were included. Positron emission tomography/CT scans were acquired for planning of SBRT. Three oncologists and three radiologists independently delineated the gross tumour volume. The interobserver variation was calculated as a mean of multiple SDs of distances to a reference contour, and calculated for the transversal plane (SDtrans) and craniocaudal (CC) direction (SDcc) separately. Concordance indexes and volume deviations were also calculated.

Results
Median tumour volume was 13.0 cm³, ranging from 0.3 to 60.4 cm³. The mean SDtrans was 0.15 cm (SD 0.08 cm) and the overall mean SDcc was 0.26 cm (SD 0.15 cm). Tumours with pleural contact had a significantly larger SDtrans than tumours surrounded by lung tissue.

Conclusions
The interobserver delineation variation was very small in this systematic cross-sectional analysis, although significantly larger in the CC direction than in the transversal plane, stressing that anisotropic margins should be applied. This study is the first to make a systematic cross-sectional analysis of delineation variation for peripheral lung tumours referred for SBRT, establishing the evidence that interobserver variation is very small for these tumours.

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Authors: Persson, G. F. (Ekstern), Nygaard, D. E. (Ekstern), Hollensen, C. (Intern), Munck af Rosenschöld, P. (Forskerdatabase), Mourtzis, L. S. (Ekstern), Due, A. K. (Ekstern), Berthelsen, A. K. (Ekstern), Nyman, J. (Ekstern), Markova, E. (Forskerdatabase), Roed, A. P. (Ekstern), Roed, H. (Ekstern), Korreman, S. (Forskerdatabase), Specht, L. (Forskerdatabase)
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Lung Tumor Segmentation Using Electric Flow Lines for Graph Cuts

Lung cancer is the most common cause of cancer-related death. A common treatment is radiotherapy where the lung tumors are irradiated with ionizing radiation. The treatment is typically fractionated, i.e. spread out over time, allowing healthy tissue to recover between treatments and allowing tumor cells to be hit in their most sensitive phase. Changes in tumors over the course of treatment allows for an adaptation of the radiotherapy plan based on 3D computer tomography imaging. This paper introduces a method for segmentation of lung tumors on consecutive computed tomography images. These images are normally only used for correction of movements. The method uses graphs based on electric flow lines. The method offers several advantages when trying to replicate manual segmentations. The method gave a dice coefficient of 0.85 and performed better than level set methods and deformable registration.
Planning and Evaluation of Radio-Therapeutic Treatment of Head-and-Neck Cancer Using PET/CT scanning

Radiation therapy relies in great extent on delineations of tumour and organs on medical images. These delineations are essential for the entire treatment. Unfortunately manual delineations are both prone to variation. At the same time the manual delineation process is time-consuming. This thesis represent a work within the automatic definition of organs and tumours. The thesis includes a summary of the prior methods employed for automatic segmentation and 3 articles describing segmentation algorithms of different areas of application for radiation therapy. Variation within and between manual and automatic segmentation methods is documented in the thesis. The last article of the thesis analyses treatment outcome difference due to manual delineation variation.

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Segmentation Using Symmetry Deviation: Abstract
Purpose: The manual delineation of gross tumour volume (GTV) for radiation therapy for head and neck cancer patients relies in some degree of pathological deviation from normal anatomical symmetry. The purpose of this study is to introduce a novel method for 3-dimensional determination of GTV and evaluate the method. The method uses deformable registration on computed tomography (CT) to find anatomical symmetry deviations of Head & Neck squamous cell carcinoma and combining it with positron emission tomography (PET) images. The method allows the use anatomical and symmetrical information of CT scans to improve automatic delineations. Materials: PET/CT scans from 30 patients were used for this study, 20 without cancer in hypopharyngeal volume and 10 with hypopharyngeal carcinoma. An head and neck atlas was created from the 20 normal patients. The atlas was created using affine and non-rigid registration of the CT-scans into a single atlas. Afterwards the standard deviation of anatomical symmetry for the 20 normal patients was evaluated using non-rigid registration and registered onto the atlas to create an atlas for normal anatomical symmetry deviation. The same non-rigid registration was used on the 10 hypopharyngeal cancer patients to find anatomical symmetry and evaluate it against the standard deviation of the normal patients to locate pathologic volumes. Combining the information with an absolute PET threshold of 3 Standard uptake value (SUV) a volume was automatically delineated. The overlap of automated segmentations on manual contours was evaluated using concordance index and sensitivity for the hypopharyngeal patients. The resulting concordance index and sensitivity was compared with the result of using a threshold of 3 SUV using a paired t-test. Results: The anatomical and symmetrical atlas was constructed. The standard deviation of the anatomical symmetry, seen in figure for one patient along CT and PET, was extracted for normal patients and compared with the deviation from cancer patients giving a new way of determining cancer pathology location. Using the novel method an overlap concordance index and sensitivity of respectively 0.43±0.15 and 0.56±0.18 was acquired. It was compared to the concordance index of segmentation using absolute threshold of 3 SUV giving respectively 0.41±0.16 and 0.51±0.19 for concordance index and sensitivity yielding p-values of 0.33 and 0.01 for a paired t-test respectively.

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Temporal Volume of Lung Tumor during Treatment with Tomotherapy

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Organisations: Image Analysis and Computer Graphics, Department of Informatics and Mathematical Modeling, University of Wisconsin-Madison, Copenhagen University Hospital
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Auto-Segmentation of Head and Neck Cancer using Textural features

Purpose: The conventional treatment for non-metastatic Head & Neck squamous cell carcinoma (HNSCC) is radiation therapy. Despite technological advances and improved efficacy, radiation therapy still relies on manual delineation of gross tumour volume which is both time consuming and prone to inter- and intra observer variability. Several automatic segmentation methods have been developed using positron emission tomography (PET) and/or computerised tomography (CT). The aim of the present study is to develop a model for 3-dimensional auto-segmentation, the level set method, to contour gross tumour volumes (GTV) in a training set of 20 HNSCC patients and evaluate its performance in an independent test set of 25 patients. Materials and Methods: 100 PET/CT textural features were extracted from manual contours of GTV on a training set. The training set consisted of PET and CT scans from 20 patients randomly selected among 45 cases with hypopharyngeal carcinoma treated with radiotherapy. All contours had been performed by experienced radiologists for treatment planning. The Jeffreys-Matusita (JM) distance, a measure of similarity between distributions, was calculated for combinations of features inside and outside the GTV respectively to choose an appropriate feature combination for segmentation of the GTV. The feature combination with the highest dissimilarity was extracted on PET and CT images from the remaining 25 HNC patients. Using these features as input for a level set segmentation method the tumours were segmented automatically. Segmentation results were evaluated against manual contours of radiologists using the DICE coefficient, and sensitivity. The result of the level set approach method was compared with threshold segmentation of PET standard uptake value (SUV) of 3 or 20% of maximal intensity and tested with a paired t-test. Results: The JM analysis determined a combination of 8 textural features as appropriate for
segmentation giving a distance of 1.1 out of 1.4. For the level set segmentation the DICE coefficient and sensitivity were 0.48±0.18 (mean ± standard deviation) and 0.57±0.24 respectively. Mean DICE coefficient for the 3 SUV and 20% intensity threshold segmentation were respectively 0.41±0.22 and 0.40±0.22, giving p-values of 0.04 and 0.02 for a higher DICE coefficient from the level set segmentation. For sensitivity the threshold segmentation yielded 0.52±0.24 and 0.51±0.26 for 3SUV and 20% intensity respectively yielding p-values of 0.01 and 0.03. Conclusion: The level set method provides a more robust and stable method for segmentation of HNSCC at hypopharynx than threshold segmentation. But it should be improved in order to resemble the manual contours of radiologist. The segmentation could serve as an initial GTV estimate for manual corrections reducing both time and variance in the process of GTV contouring.

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Organisations: Department of Informatics and Mathematical Modeling, Image Analysis and Computer Graphics, Department of Electrical Engineering, Biomedical Engineering, Copenhagen University Hospital
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Inter-observer delineation uncertainty in radiotherapy of peripheral lung tumors

Introduction: Delineation uncertainties are important as they contribute to systematic errors and can lead to geographical miss of the target. As the true gross tumour volume (GTV) is unknown, delineation error can only be estimated. In this study we evaluate the inter-observer delineation variation for peripheral lung tumours in our clinic with the aim of designing appropriate population based treatment margins. Patients and methods: A cohort of 22 (all) patients referred for stereotactic radiotherapy of early lung cancer or lung metastasis (total of 26 tumours) in our clinic in 2008 was included in the study. In our clinical protocol contrast enhanced PET/CT scan is primarily analysed by a specialist in nuclear medicine and a radiologist together. The PET positive volume is delineated by the specialist in nuclear medicine and only the CT scan and this contour is imported to Eclipse (Varian Medical Systems) where GTV delineation is done by an oncologist and a radiologist together. In this study delineations were done independently, with a fixed broad window (-1000 to 700 HU), by three clinical oncologists and three radiologists. For each slice the centre of volume (CoV) of all contours was identified. For each patient the standard deviation of the distances from the CoV to each contour in 24 equally spaced angles in all slices (SDtrans) was considered a measure for inter-observer delineation uncertainty in the transversal plane. For the cranio-caudal (CC) direction the centre of the CoV of all contours was calculated and the distance from this centre of CoV to the most cranial and the most caudal slice of each contour was found. For each patient the SD of the absolute value of these distances (SDcc) gives a measure of the inter-observer delineation variation in the CC-direction. The means of SDtrans and SDCC respectively for all tumours were considered measures of the inter-observer delineation uncertainties for our clinic. All analysis was done in MatLab version 2007b. Results: Results are listed in table 1. The overall interobserver uncertainties were 0.14 mm (SDtrans) and 0.26 mm (SDCC), and the uncertainties were significantly larger for the radiologists compared to the oncologists in both directions (Wilcoxon signed rank test, two-tailed significance level, p <0.05). Conclusion: The inter-observer uncertainties in this study are small compared to earlier, similar studies. This is probably caused by the very homogeneous patient population, the uniform use of PET information and that all observers except one were recruited from the same institution. Nevertheless, delineation error contributes to the highly weighted systematic part of the probabilistic margin computation, and remains a major source of uncertainty in modern radiotherapy, where set-up uncertainties have been significantly reduced.

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lung tumor, Delineation, radiotherapy, uncertainty
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Segmenting the Parotid Gland using Registration and Level Set Methods

The bilateral parotid glands were segmented using a registration scheme followed by level set segmentation. A training set consisting of computerized tomography from 10 patients with segmentation of the bilateral glands were used to optimize the parameters of registration and level set segmentation. The method was evaluated on a test set consisting of 8 corresponding data sets. The attained total volume Dice coefficient and mean Hausdorff distance were 0.61 ± 0.20 and 15.6 ± 7.4 mm respectively. The method has improvement potential which could be exploited in order for clinical introduction.

Variability of textural features in FDG PET images due to different acquisition modes and reconstruction parameters

Background. Characterization of textural features (spatial distributions of image intensity levels) has been considered as a tool for automatic tumor segmentation. The purpose of this work is to study the variability of the textural features in PET images due to different acquisition modes and reconstruction parameters. Material and methods. Twenty patients with solid tumors underwent PET/CT scans on a GE Discovery VCT scanner, 45-60 minutes post-injection of 10 mCi of [F-18]FDG. Scans were acquired in both 2D and 3D modes. For each acquisition the raw PET data was reconstructed using five different reconstruction parameters. Lesions were segmented on a default image using the threshold of 40% of maximum SUV. Fifty different texture features were calculated inside the tumors. The range of variations of the features were calculated with respect to the average value. Results. Fifty textural features were classified based on the range of variation in three categories: small, intermediate and large variability. Features with small variability (range 30%). Conclusion. Textural features such as entropy-first order, energy, maximal correlation coefficient, and low-gray level run emphasis exhibited small variations due to different acquisition modes and reconstruction parameters. Features with low level of variations are better candidates for reproducible tumor segmentation. Even though features such as contrast-NGT, coarseness, homogeneity, and busyness have been previously used, our data indicated that these features presented large variations, therefore they could not be considered as a good candidates for tumor segmentation.
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Projects:

Planning and evaluation of radio-therapeutic treatment of head-and-neck cancer using PET/CT scanning

Department of Informatics and Mathematical Modeling
Period: 01/08/2009 → 19/12/2012
Number of participants: 7
Phd Student:
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Supervisor:
Hejgaard, Liselotte (Intern)
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Main Supervisor:
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Pausen, Rasmus Reinhold (Intern)
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