Computer assisted analysis of lung tumor regression during radiotherapy

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Abstract

Lung tumors can regress substantially during radiotherapy which suggests that it may be beneficial to perform adaptive replanning during the treatment. However, the regression of visible disease is not necessarily consistent with the regression of microscopic disease and reduction of the target volume should follow a detailed analysis of regression of tumor border and nearby structures. We developed an algorithm based on elastic registration to assist this analysis. The algorithm can discriminate between elastic and non-elastic regression, i.e., tumor border regression that is consistent or inconsistent with the motion of nearby structures.

Keywords

Adaptive radiation therapy, tumor regression, elastic registration, cone-beam computed tomography.

Introduction

Adaptive radiation therapy (ART) [1] has rapidly developed with the advent of in-room imaging such as cone-beam (CB) computed tomography (CT) [2]. Most current clinical protocols aim at minimizing setup errors but more gain can be expected by re-planning patients which anatomy substantially changes during the treatment. This work focuses more specifically on accounting for the regression of lung tumors in ART.

Substantial regression of lung tumors has been observed during radiotherapy in previous studies [3, 4, 5, 6, 7, 8]. This fact has lead to re-planning studies using a new gross tumor volume (GTV) delineated on a repeat CT acquired during the treatment [9, 10]. In these studies, the GTV was expanded to the clinical target volume (CTV) using the same margin for the adapted plan as for the initial plan. Therefore, the assumption is that microscopic disease (CTV) has regressed in the same way as macroscopic disease (GTV). In other words, the assumption is that the invisible malignant tissues have regressed consistently with the visible ones. To our knowledge, there are no publications to support this assumption.

Microscopic extension can not be visualized on macroscopic imaging (CT, PET or MRI). Only histopathologic studies of operated patients provide knowledge on the extent of microscopic infiltration. As a surrogate, van Zwienen *et al* [8] have proposed to analyze the motion of anatomical structures next to the border of regressing tumors. In some patients, the structures move along with the GTV border, which suggests that healthy tissues have moved in the original CTV and that CTV reduction could be beneficial. However, in other cases, the surrounding tissue does not follow the GTV border and there is no indication that tissues initially identified as infiltrated have regressed.

In this work, we developed an algorithm to assist the clinical analysis with an automated quantification of the consistency between the regression of the tumor border and the motion of nearby structures.

Methods and Materials

Definitions

We define two types of tumor regression observed by comparing two CT images acquired at different fractions during the radiation treatment (Fig. 1). An *elastic regression* is a regression of the tumor which is consistent with the motion of structures next to the tumor border. Oppositely, a *non-elastic regression* is a regression of the tumor which is not consistent with the motion of structures next to the tumor border. The consistency of the motion of two neighboring structures (the tumor border and the nearby

structures here) is defined according to an elastic registration algorithm, hence the naming of the regression types.

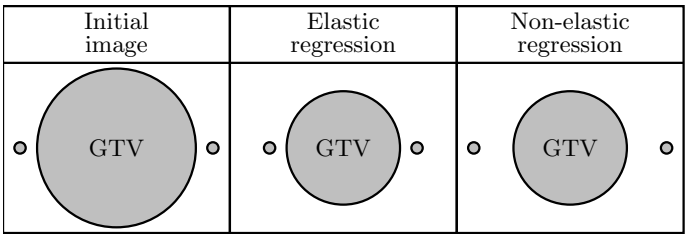

Figure 1: Schematic illustration of the two types of GTV regression.

Elastic registration algorithm

Elastic registration, also known as deformable registration, aims at finding the non-linear mapping function between two images by computing an optimal balance between similarity of the mapped images and smoothness of the mapping function. We used a multiresolution B-spline registration algorithm with the normalized cross correlation as similarity measure and no additional constraints on the smoothness of the mapping function. 3 levels of resolution were used for the B-spline control points. Their finest spacing was isotropic and equal to 1 cm.

Elastic consistency measure

We hypothesized the following: if the motion of a structure is elastically consistent with the motion of nearby structures, elastic registration will produce the same result whether this structure is included or not in the similarity measure during registration. From this assumption, the elastic consistency of the motion of a structure with its neighborhood can be quantified through the computation of the difference between the two outputs of an elastic registration algorithm obtained with and without the structure in the similarity measure during registration. The difference is null when the motion is consistent and differs from 0 when the motion is inconsistent.

We straightforwardly translated this generic solution to the particular case of tumor regression. The aim was to estimate if the regression of the GTV, i.e. the motion of the GTV border, was consistent with the motion of nearby structures. We performed two elastic registrations, one with and one without the GTV in the similarity measure. The amplitude of the difference between the two vector fields was overlayed as a colorwash on the CBCT images for spatial measurement of the consistency.

Test dataset

Two characteristic lung patients were selected from a previous study on anatomical changes in lung patients [8]. Repeat CBCT images were acquired during the treatment for setup correction. CBCT images were reconstructed with motion compensation to correct for respiration artifacts [11]. The first and the last CBCT images of each patient, acquired with an interval of about one month, were used for analyzing the tumor regression. The last CBCT was initially registered on the first CBCT using rigid registration of the bony anatomy. The ROI excluded during elastic registration was drawn such that it encompassed the GTV on the first CBCT but not the nearby structures.

Results

Fig. 2 illustrates a tumor with mostly elastic regression. The lung structures on the posterior side of the GTV moved along with the GTV border. This behavior was confirmed by the amplitude of the difference vector field between the two registrations overlaid as a color wash: no inconsistency superior to 2 mm was observed between the motion of the GTV border and the motion of nearby posterior structures. The colorwash also showed differences around the thoracic wall which indicated that the regressing tumor slid along the thoracic wall, i.e. that the ribs did not move consistently with the tumor border. Finally, non-elastic regression was observed on the caudal side of the tumor.

Fig. 3 illustrates a tumor with mostly non-elastic regression. The lung structures around the initial GTV did not move consistently with the GTV border but stayed close to their initial location. Therefore, the first registration mapped the tumor borders and had to find a compromise with nearby structures, while the second registration mapped nearby structures without compromising with the GTV border. Consequently, the amplitude of the difference vector field was superior to 2 mm in a rim surrounding the ROI used by the method. The difference was the highest at the border and decreased gradually.

Discussion and Conclusions

We developed an algorithm to measure the consistency of GTV regression with the motion of nearby structures using elastic registration. When the regression was elastic, no differences were observed whether the GTV was included or not in the registration (Fig. 2). When the regression was non-elastic,

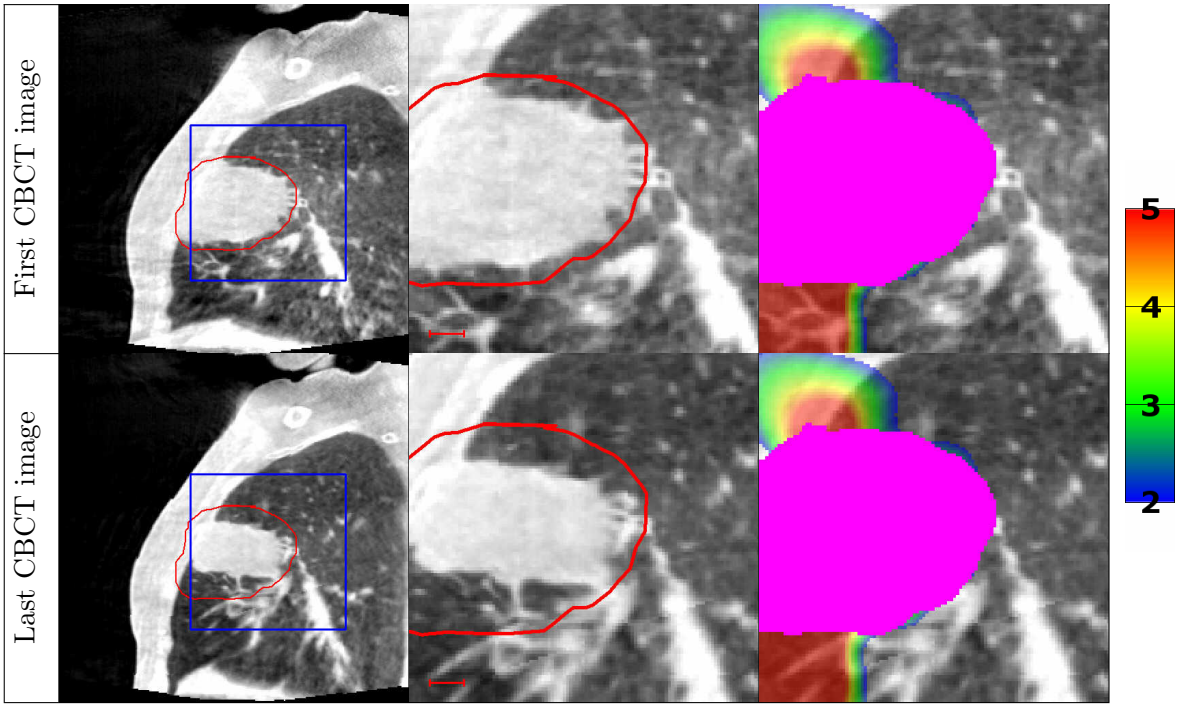

Figure 2: Example of a tumor with mostly elastic regression. The red contour is the contour of the mask used to exclude the GTV from the registration. Left: full sagittal slice of the CBCT image. Middle: zoom in the squared ROI drawn in the left column with a 1 cm scale. Right: idem with the mask overlaid in opaque purple and the amplitude of the difference vector field (between the elastic registration with and without the GTV) overlaid as a colorwash (scale in mm).

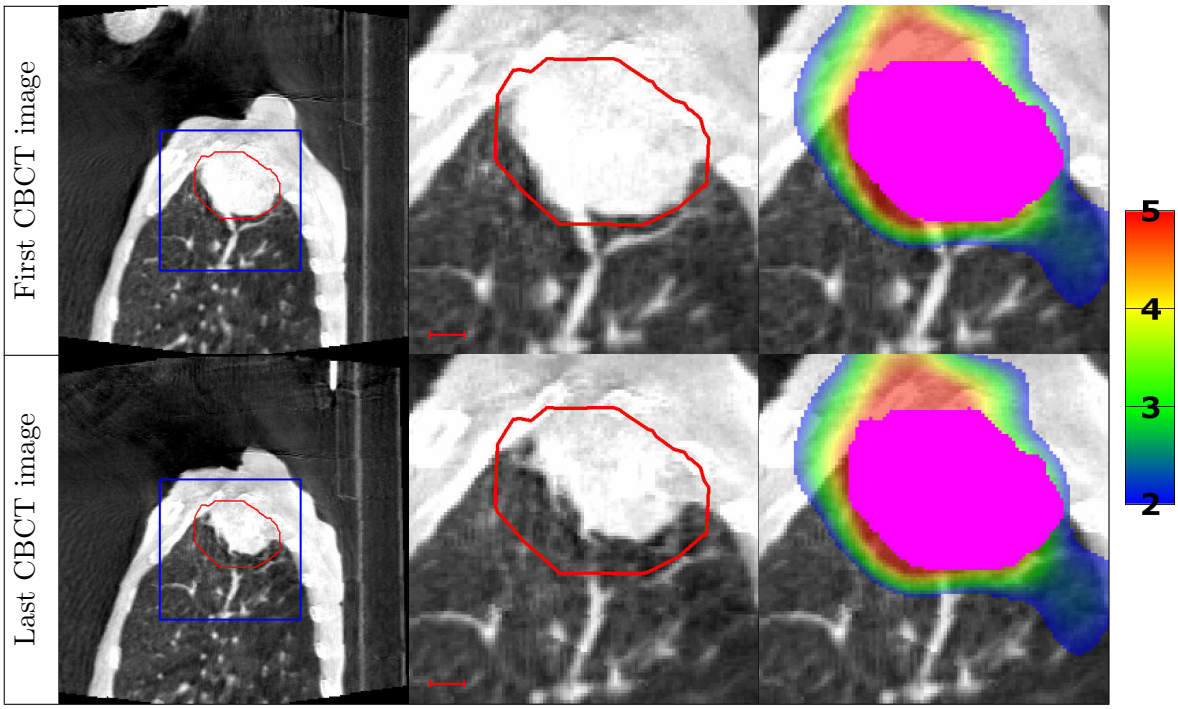

Figure 3: Idem as Fig. 2 for a tumor with mostly non-elastic regression.

the elastic registration had to compromise between the GTV border and the motion of nearby structures which resulted in differences with the elastic registration excluding the GTV (Fig. 3).

The algorithm relies on the assumption that the GTV border influences the registration of nearby structures which is a typical behavior of elastic registration. Nevertheless, a clear GTV border and visible adjacent structures are required to reliably analyze the regression. If not, it is not possible to evaluate the type of regression, which is also true for non-assisted visual analysis.

The consistency measure is strongly related to the algorithm used for non-elastic registration and its parameterization. In particular, the constraint on the smoothness of the mapping function drives the extent of the influence of the GTV border on the registration of nearby structures. Therefore, the size of the inconsistency rim measured for non-elastic regression is related to the chosen registration algorithm and its parameterization. We used the default parameters of our in-house implementation but each implementation is likely to produce a different answer.

The selected examples illustrate the variety of lung tumor regressions. The best way to handle tumor regression in ART is currently not known. Replanning on smaller volumes is safer for elastic regression than non-elastic regression because healthy tissues have moved in the initial target volume. However, the overlays in Fig. 2 and 3 show that the behavior is not binary. Clinical decision on replanning must account for the complexity of tumor regression and the algorithm developed in this study can assist it.

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