Radiotherapy and Oncology 123 (2017) 363–369

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Lung cancer radiotherapy

Survival prediction of non-small cell lung cancer patients using radiomics analyses of cone-beam CT images

Janna E. van Timmeren [a,*], Ralph T.H. Leijenaar [a], Wouter van Elmpt [a], Bart Reymen [a], Cary Oberije [a], René Monshouwer [b], Johan Bussink [b], Carsten Brink [c,d], Olfred Hansen [c,d,e], Philippe Lambin [a]

[a] Department of Radiation Oncology (MAASTRO), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre (MUMC); [b] Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, The Netherlands; [c] Institute of Clinical Research, University of Southern Denmark, Odense; [d] Laboratory of Radiation Physics, Odense University Hospital; and [e] Department of Oncology, Odense University Hospital, Denmark

ARTICLE INFO

Article history:
Received 2 January 2017
Received in revised form 20 March 2017
Accepted 17 April 2017
Available online 12 May 2017

Keywords:
Radiomics
Computed tomography
Cone-beam CT
Non-small cell lung cancer
Survival prediction

ABSTRACT

Background and purpose: In this study we investigated the interchangeability of planning CT and cone-beam CT (CBCT) extracted radiomic features. Furthermore, a previously described CT based prognostic radiomic signature for non-small cell lung cancer (NSCLC) patients using CBCT based features was validated.

Material and methods: One training dataset of 132 and two validation datasets of 62 and 94 stage I–IV NSCLC patients were included. Interchangeability was assessed by performing a linear regression on CT and CBCT extracted features. A two-step correction was applied prior to model validation of a previously published radiomic signature.

Results: 13.3% (149 out of 1119) of the radiomic features, including all features of the previously published radiomic signature, showed an R^2 above 0.85 between intermodal imaging techniques. For the radiomic signature, Kaplan–Meier curves were significantly different between groups with high and low prognostic value for both modalities. Harrell's concordance index was 0.69 for CT and 0.66 for CBCT models for dataset 1.

Conclusions: The results show that a subset of radiomic features extracted from CT and CBCT images are interchangeable using simple linear regression. Moreover, a previously developed radiomics signature has prognostic value for overall survival in three CBCT cohorts, showing the potential of CBCT radiomics to be used as prognostic imaging biomarker.

With 1.6 million deaths in 2012, lung cancer is the most common cause of death from cancer worldwide [1,2]. Lung cancer is also the most frequently diagnosed cancer with 1.82 million new cases in 2012, comprising 12.9% of the worldwide incidence. Improved disease outcome and a subsequent increase in a patient's chance of survival can be achieved by individualized treatment [3–5]. To this end, biomarkers are needed [6,7].

Medical imaging has become a cornerstone of personalized cancer treatment over the past decades. Novel advanced imaging analysis techniques such as radiomics – extracting quantitative features from medical images such as computed tomography (CT), positron emission tomography (PET), or magnetic resonance imaging (MRI) – can identify a patient's response to treatment or the probability of developing side effects [3,8–14].

Furthermore, a longitudinal approach where the change of quantitative radiomic features (i.e. delta radiomics) is examined, may also aid in early response assessment compared to the use of only baseline (imaging) characteristics [15–17]. However, in most studies, PET-, CT- or MRI-scans are only performed at baseline or at very limited number of points in time, hampering the possibility for timely treatment adaptation. However, during radiotherapy for NSCLC patients, three-dimensional (3D) cone-beam CT (CBCT) images are routinely obtained for patient set-up and positioning verification [18]. These images could provide valuable information about day-to-day changes of the tumor during the course of treatment [19].

Radiomics based on CBCT imaging therefore offers a possibility for (early) treatment adaptation using the changes of imaging biomarkers over time. Where the prognostic value of conventional

* Corresponding author at: Department of Radiation Oncology (MAASTRO Clinic), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, Dr. Tanslaan 12, 6229 ET Maastricht, The Netherlands.
E-mail address: janita.vantimmeren@maastro.nl (J.E. van Timmeren).

http://dx.doi.org/10.1016/j.radonc.2017.04.016
0167-8140/

CT images is already known [9,11,20], the potential of CBCT radiomics still needs to be investigated especially because image quality of CBCT is generally worse compared to conventional CT images. Therefore, in this study we aimed to compare radiomics for CT and CBCT by investigating the interchangeability of radiomic features extracted from both modalities. Furthermore, we validated a previously published CT-based radiomics signature (a Cox regression model based on imaging only, without clinical parameters) [20,21], using three independent CBCT datasets to validate the model and to evaluate the prognostic potential of CBCT imaging compared to CT imaging.

Methods and materials

Patients

Three NSCLC cohorts from three different institutes were included in this study. All patients received radiation therapy with curative intent. Patients that received less than 40 Gy were excluded from the analysis. Moreover, patients referred to postoperative radiotherapy or simultaneous treatment of brain metastases were excluded, as well as patients with prior history of lung cancer.

The first dataset consists of 132 stage I-IV patients treated between January 2012 and January 2014 at Maastro Clinic, Maastricht, the Netherlands. Data are provided online on www.cancerdata.org [22]. The second dataset consists of 62 stage I-IIIB patients receiving treatment between January 2009 and January 2011 at Radboud University Medical Center, Nijmegen, the Netherlands. The third dataset consists of 94 stage I-IIIB patients, a subset of the cohort used in a previous study on CBCT imaging [19], treated between November 2007 and December 2011 at Odense University Hospital, Odense, Denmark. This retrospective study was approved by each respective institutional review board.

Image acquisition

The images of the treatment planning CT (pCT) scan and the images of the cone-beam CT (CBCT) scan prior to the first radiotherapy fraction were used for all analyses in this study. Details of all image acquisitions can be found in the Supplementary Material.

Feature extraction

The gross tumor volume (GTV) of the primary tumor was manually delineated on the CT scan by experienced radiation oncologists and used for treatment planning. For each patient, the GTV was registered to the CBCT image using a deformable transformation field obtained by performing non-rigid registration of the pCT image and the CBCT image [23,24]. Afterward, all contours were visually checked and manually adjusted when necessary by an experienced radiation oncologist.

Radiomic features were extracted from the delineated tumor regions of the pCT and CBCT images. A total of 1119 radiomic features were calculated, divided into five groups: tumor intensity ($n = 19$), texture ($n = 95$), wavelet ($n = 912$), Laplacian of Gaussian ($n = 74$), and shape ($n = 19$). Emphasis was placed on the features of the previously published prognostic radiomic signature: I) tumor intensity: 'Energy', II) texture: 'Gray Level Nonuniformity, III) wavelet: 'Gray Level Nonuniformity HLH', and IV) shape: 'Compactness' [20]. All features were automatically extracted using in–house developed software, using Matlab 2014a (MathWorks, Natick, Massachusetts, U.S.A.). A mathematical description of all features can be found at the end of the Supplementary Material.

Correction

A two-step correction procedure was performed on CBCT prior to model validation, which will be explained in further detail below. The first step comprises an intensity value correction and the second step is a radiomic feature normalization. The workflow of correcting CBCT is shown in Fig. 1.

Step 1, the intensity correction, was performed to equalize the distribution of the intensity levels between CBCT images. To find the correction factor, the mean intensity level in a region of interest (ROI) of approximately 5 cm^2 in the heart was derived for each patient in the CBCT image. This ROI was chosen because typical Hounsfield units were known and because an area of this size at that location could be drawn for all images. The reference value was set to 50 HU, since according to literature typical Hounsfield units in myocardium and blood are between 40 and 60 HU [25]. A scaling factor was calculated using (mean intensity level + 1000)/(reference value + 1000). Correction factors, derived for individual patients, were multiplied with intensity levels of CBCT images prior to feature extraction. In this study we decided to apply the intensity correction for all images, instead of defining a certain range around the reference value of 50 HU within which some intensity values could be accepted.

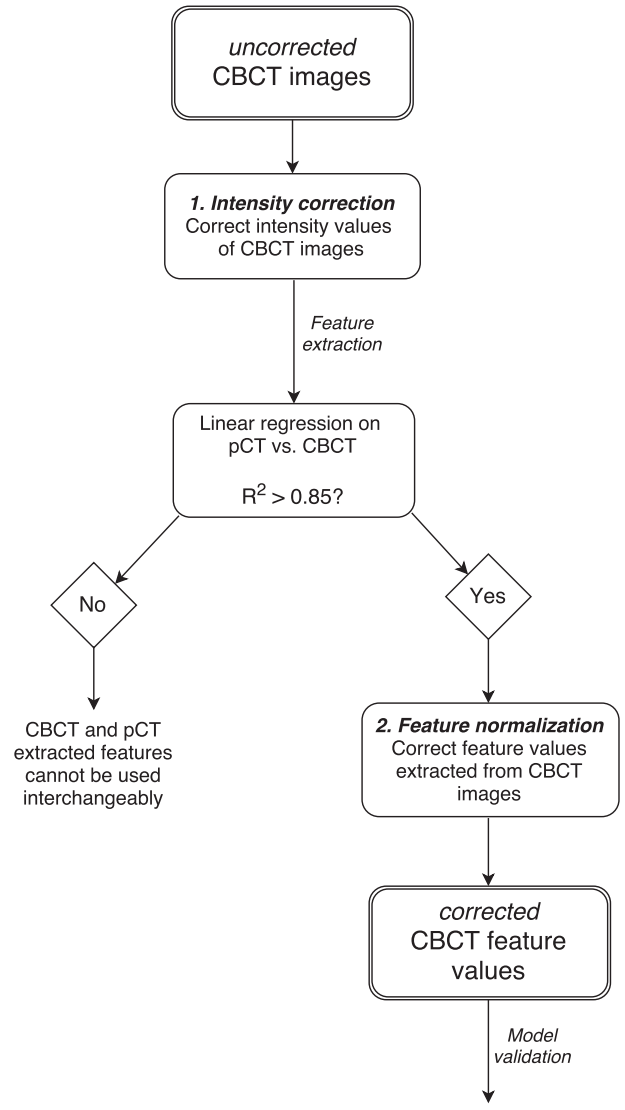

Fig. 1. Workflow. Workflow of two-step correction of CBCT images and extracted features prior to model validation.