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Original paper

Exploration of temporal stability and prognostic power of radiomic features based on electronic portal imaging device images

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ABSTRACT

Purpose: We aimed to explore the temporal stability of radiomic features in the presence of tumor motion and the prognostic powers of temporally stable features.
Methods: We selected single fraction dynamic electronic portal imaging device (EPID) (n = 275 frames) and static digitally reconstructed radiographs (DRRs) of 11 lung cancer patients, who received stereotactic body radiation therapy (SBRT) under free breathing. Forty-seven statistical radiomic features, which consisted of 14 histogram-based features and 33 texture features derived from the graylevel co-occurrence and graylevel run-length matrices, were computed. The temporal stability was assessed by using a multiplication of the intra-class correlation coefficients (ICCs) between features derived from the EPID and DRR images at three quantization levels. The prognostic powers of the features were investigated using a different database of lung cancer patients (n = 221) based on a Kaplan-Meier survival analysis.
Results: Fifteen radiomic features were found to be temporally stable for various quantization levels. Among these features, seven features have shown potentials for prognostic prediction in lung cancer patients.
Conclusions: This study suggests a novel approach to select temporally stable radiomic features, which could hold prognostic powers in lung cancer patients.

1. Introduction

Radiomics is a novel field that massively and comprehensively analyzes a large number of medical images, and extracts mineable data (phenotypic features) that can make it possible to practically carry out precision medicine [1,2]. A primary function of the radiomic features decoding tumor phenotypes is to characterize intra-tumor heterogeneity, which is associated with the therapeutic response of cancer patients [3,4], by quantifying the spatial relationship between image pixels/voxels [2,5], thereby representing the inhomogeneous distribution of pixel/voxel values.

The assessment of the temporal stability, i.e. the consistency of the feature values against temporal variability sources in multi-dimensional medical images, is essential for the development of robust prognostic models based on the temporally stable radiomic features. The radiomic features were extracted from images acquired by various imaging modalities, mainly diagnostic or treatment planning computed tomography (CT) [5–7], and 18^{F}-fluorodeoxyglucose positron emission tomography (FDG-PET) for lung cancer patients [8,9]. In CT images, radiomic features have shown robustness against variability in image characteristics such as number of graylevels [7] and image reconstruction algorithms [10]. However, a few studies have investigated the temporal stability of the radiomic features within intervals of 15 min [6], or in images including time-varying events such as the injection of contrast-enhancement materials [11] or respiratory motion [12]. Fave et al. have investigated the stability of 68 radiomic features against tumor motion; however, the evaluation was performed on two test–retest image sets acquired with 15 min intervals, as well as on cone beam CT (CBCT) images of a tumor texture insert with simulated unidirectional displacements [13].

Radiomic features comprise several types of image features including statistical features. A recent systematic review [14], which was based on 97 relevant research papers, have reported several associations between statistical features and tumor characteristics including tumor stage [6], metastasis [15], treatment response [16] and genetic content of lung cancers [6,17]. The statistical features can be classified

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into two subtypes, i.e. histogram-based features and texture features. The histogram-based features are derived from the histogram of the image, which demonstrates the grayscale levels (quantization levels) with their occurrence frequencies within a defined region-of-interest (ROI). Thus, the histogram-based features are overall descriptors of the distribution of the quantization levels in the ROI, without considering the spatial relationships between the quantization levels. The texture features emphasize the local distribution of the quantization levels within the ROI. A graylevel co-occurrence matrix (GLCM), which is used for deriving the textural features, is built by using the number, distance and angle of quantization level combinations in the image [18]. Another matrix is the graylevel run-length matrix (GLRLM) which includes the frequency of pixels/voxels sequences with similar quantization levels in all directions [19]. All statistical features are dependent on the number of grayscale or quantization levels. Therefore, temporally stable radiomic features were explored with taking into account the robustness of various numbers of quantization levels in this study.

Temporally stable features may be independent, i.e. robust against changes in pixel/voxel values caused by a tumor motion. Up to our knowledge, no studies have investigated the temporal stability of the radiomic features with relatively higher frame rates using dynamic portal images, e.g. electronic portal imaging device (EPID) images. Therefore, the purpose of this study was to assess the temporal stability of radiomic features based on EPID images. Since the prognosis prediction, in terms of prediction of the overall survival probability, has been an important end-point of radiomic approaches [6,12,14,20], this study attempted to select temporally stable radiomic features possessing prognostic powers.

2. Materials and Methods

2.1. Clinical cases

This retrospective study was performed under a protocol approved by the institutional review board of our university hospital. Eleven patients with clinically diagnosed lung cancers, who received stereotactic body radiation therapy (SBRT) from 2013 to 2015, were selected for this study. The patients' characteristics are summarized in Table 1. Nine patients received 48 Gy/4 fractions and 2 patients received 54 Gy/4 fractions, prescribed at isocenters in four fractions, with an accelerating voltage of 6 MV on a linear accelerator (Clinac 21EX; Varian Medical Systems Inc., Palo Alto, USA). The dose was delivered with a dose rate of 600 MU/min under free-breathing in two beam angles conformal with a fixed geometry. All patients were treated with the same linear accelerator.

In this study, EPID images and digitally reconstructed radiographs (DRRs) were used as dynamic and static portal images, respectively. The EPID images were acquired by using an amorphous silicon EPID (Portal Vision aS-1000; Varian Medical Systems Inc., Palo Alto, USA) with 16-bit quantization levels and a matrix size of 1024 × 768 pixels, pixel size of 0.39 mm and a frame rate of 13.0 frames/s on average. The EPID images were acquired at the cine mode during the treatment time of the four radiation treatment fractions. The number of frames acquired for each patient at each fraction is shown in Table 1. The mean and total number of acquired frames for each session in all the patients were 83.09 and 914 frames, respectively. All the EPID images were acquired with the same EPID panel. For consistency, sequences of 25 frames/case from the EPID images acquired at the first treatment fraction for each patient were selected for analysis of the temporal stability of the radiomic features.

In our institution, the EPID has been calibrated for removing background noise and providing a linear and spatially uniform energy response for the EPID images. The detector response was calibrated once a month by acquiring flood field and dark field images. The flood field image was acquired by the uniform irradiation of the EPID, and was used for adjusting the differences in pixel sensitivities. The dark field image was acquired by averaging a sequence of 20 frames without irradiation, and was used for calculating the off-set of the pixel values. A beam profile for off-axis correction provided by the linac's manufacturer was used in the flood field calibration. The exposure MU was used as a calibrated unit, and the calibration was performed by setting the EPID at the isocenter plane with a source-to-detector distance of 100 cm while irradiating the EPID with 100 MU with a beam energy of 6 MV.

The DRRs were reconstructed from the planning CT images which were acquired at free-breathing. The planning CT images were acquired by using a 4-slice CT scanner (Mx 8000; Philips, Amsterdam, The Netherlands) with 12-bit quantization levels, a matrix size of 512 × 512 pixels, and a slice thickness of 2.0 mm. The radiation treatment plans including delineations of the gross tumor volume (GTV) on the planning CT image were made based on a consensus between two experienced radiation oncologists using a commercial treatment planning system (Eclipse, Varian Medical Systems Inc., Palo Alto, USA). The internal target volume (ITV) margin was defined for each patient based on a 4D CT scan. First, GTVs were delineated at images in the end-of-exhale (EE) and end-of-inhale (EI) phases of the respiratory cycle. The ITV was then computed as the OR region of the two GTVs, and the calculated volume was used for defining the ITV in the planning CT image. The clinical target volume (CTV) was defined as the ITV plus 2 mm around it. The planning target volume (PTV) was defined as the CTV plus a setup margin of 5 mm around it. The prescribed dose was defined as the minimum dose received by 95% of the PTV. Further details on the reconstruction of the image were described in Refs. [21,22]. The geometric setting conformed to that of the EPID mounted on the linear accelerator. In order to avoid the anatomical structures overlapping with the tumor regions (e.g. ribs and heart), only images

Table 1
Characteristics of clinical cases used in this study.

Patient No.	Gantry angle (°)	Age	Sex	Tumor location	Tumor size (major axis; mm)	Histology	TNM grade	Tumor type	Prescribed dose/No. of fractions (Gy/Fr)	Total number of frames per fraction
1	180	86	M	RLL	20	Unknown	cT1aN0M0	Solid	48/4	65
2	195	78	F	RUL	15	N/A	cT1aN0M0	GGO	48/4	81
3	190	77	M	RUL	8	META (N/C)	No record	Solid	48/4	86
4	195	78	M	RUL	23	ADN	cT2aN0M0	Solid	54/4	77
5	180	84	M	RUL	20	Unknown	cT1bN0M0	Mixed GGO	48/4	97
6	180	67	M	RUL	8	META (N/C)	No record	Solid	48/4	83
7	180	70	M	RLL	12	Unknown	No record	GGO	48/4	64
8	170	83	F	RLL	20	SCC	cT1aN0M0	Solid	48/4	63
9	170	87	F	RUL	15	Unknown	No record	GGO	48/4	74
10	180	76	M	RUL	24	REC (N/C)	No record	Solid	48/4	90
11	197	58	M	RUL	14	META (N/C)	No record	Solid	54/4	134

M: Male; F: Female; RUL: Right-Upper Lobe; RLL: Right-Lower Lobe; GGO: Ground Glass Opacity; SCC: Squamous Cell Carcinoma; ADN: Adenocarcinoma; META: Metastasis; REC: Recurrence; N/C: Not confirmed.