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Biomarkers for lung SBRT

CT-based radiomic analysis of stereotactic body radiation therapy patients with lung cancer

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ABSTRACT

Background: Radiomics uses a large number of quantitative imaging features that describe the tumor phenotype to develop imaging biomarkers for clinical outcomes. Radiomic analysis of pre-treatment computed-tomography (CT) scans was investigated to identify imaging predictors of clinical outcomes in early stage non-small cell lung cancer (NSCLC) patients treated with stereotactic body radiation therapy (SBRT).

Materials and methods: CT images of 113 stage I-II NSCLC patients treated with SBRT were analyzed. Twelve radiomic features were selected based on stability and variance. The association of features with clinical outcomes and their prognostic value (using the concordance index (CI)) was evaluated. Radiomic features were compared with conventional imaging metrics (tumor volume and diameter) and clinical parameters.

Results: Overall survival was associated with two conventional features (volume and diameter) and two radiomic features (LoG 3D run low gray level short run emphasis and stats median). One radiomic feature (Wavelet LLH stats range) was significantly prognostic for distant metastasis (CI = 0.67, q-value < 0.1), while none of the conventional and clinical parameters were. Three conventional and four radiomic features were prognostic for overall survival.

Conclusion: This exploratory analysis demonstrates that radiomic features have potential to be prognostic for some outcomes that conventional imaging metrics cannot predict in SBRT patients.

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Heterogeneous disease within and among patients demands a need for an individualized approach to cancer treatment. Precision medicine aims to design treatment plans tailored to the specific disease profile of the patient to improve outcomes. However, a major challenge for individualized treatment is the inability to accurately predict how a patient's disease will behave and respond to particular therapies prior to treatment [1].

Treatment plans for cancer patients involve one or several treatment modalities involving surgery, chemotherapy and/or radiation therapy (RT). For early stage non-small cell lung cancer (NSCLC) patients, the primary treatment is surgery [2]; however, due to underlying comorbidities, medically inoperable patients are treated with hypofractionated RT, known as stereotactic body radiation therapy (SBRT), as the standard of care [3]. Compared to conventional RT, SBRT administers higher radiation doses over a hypofractionated scheme (e.g. 2 Gy/fraction over 30 fractions for conventional RT vs. 12–18 Gy/fraction over 3–5 fractions for SBRT). SBRT has demonstrated excellent local control, overall survival (OS) and cancer-specific survival (CSS). These promising treatment outcomes have motivated investigations comparing the efficacy of SBRT to surgery, as a potential alternative treatment for surgical candidates [4]. However, despite the successes of SBRT, some patients still develop distant metastases (DM) (13–23%) and local recurrence (4–14%) [5–11]. While early stage patients with larger tumors (i.e. overall stage IB-IIA) who undergo surgical resection may receive adjuvant chemotherapy [12], patients with medically inoperable disease often have comorbidities that limit their ability to tolerate systemic therapy. Therefore, systemic therapy is not a feasible global strategy for all SBRT patients and there is a need for a non-invasive patient stratification approach to identify those who are at highest risk of recurrence after SBRT. Identification of these patients prior to treatment would allow augmentation of their therapeutic approach with addition of systemic therapy and/or radiation dose intensification to reduce disease relapse rates and increase OS [13].

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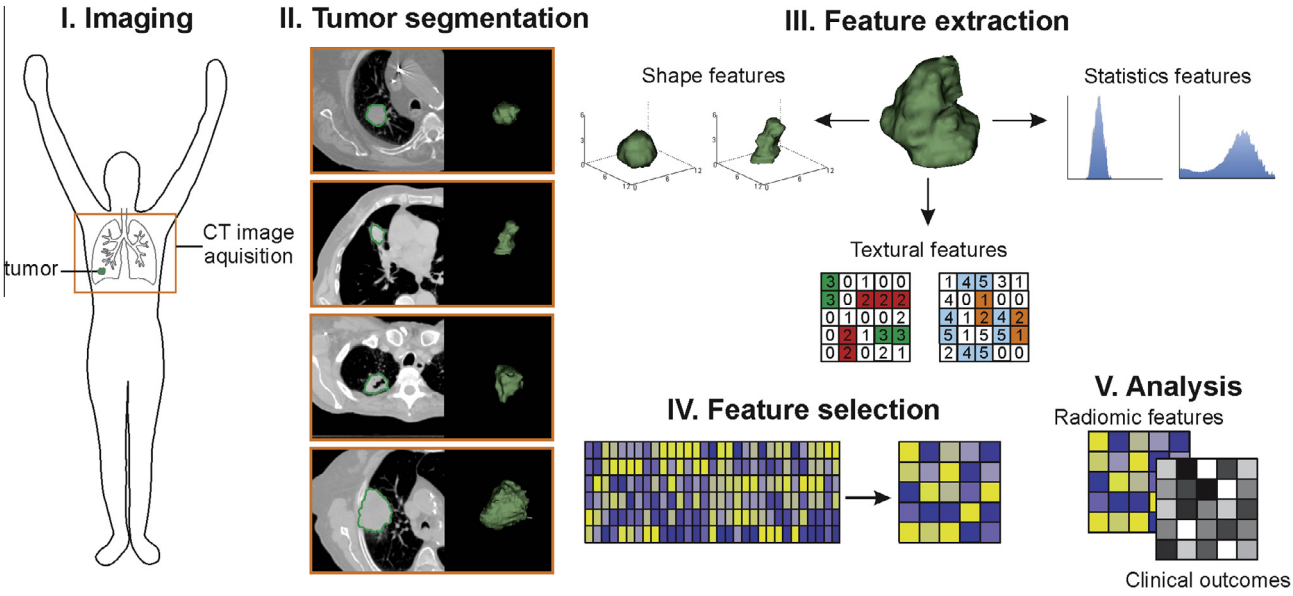

Fig. 1. Schematic of the radiomics workflow. (I) Computed tomography (CT) images of the lung are acquired of the patient. (II) Primary tumors are segmented. (III) Radiomics features are extracted from the whole tumor volume. (IV) The high-dimensional feature set is reduced to a low-dimensional feature set solely based on stability and variance using a data-driven approach. (V) The radiomic features and clinical outcomes are analyzed to determine their prognostic value.

A novel method to classify patients could be based on their tumor phenotype derived from medical imaging. Radiomics offers a non-invasive approach to precision medicine by extracting a large number of advanced quantitative features from medical images to assess the tumor phenotype [1,14,15]. It then involves comprehensive analyses of these features with clinical outcomes as potential prognostic indicators using robust and reproducible methodology [16–18] (Fig. 1). Radiomics generates a unique imaging atlas of the tumor that is a quantification of the tumor phenotype and could provide superior prognostic power over current clinical imaging metrics (e.g. tumor diameter as a predictor of response). Radiomic features have been associated with tumor characteristics, such as genotype and protein expression [19–21], and have been prognostic of clinical outcomes [22–26].

Computed tomography (CT)-based radiomics has immense potential for developing imaging biomarkers for NSCLC patients treated with SBRT since it is the most widely used imaging modality in RT for treatment planning, guidance and follow-up. While quantitative CT imaging has been well reported for lung cancer diagnosis and management [27], there are a limited number of studies on predicting outcomes in lung cancer patients undergoing SBRT [28–32]. Analysis of baseline Hounsfield Units (HU) and changes in HU or textural features after SBRT have been investigated as prognostic indicators for radiation-induced lung damage [28–30,32] and recurrence [31]. These studies have been limited in their reproducibility and prognostic power prior to SBRT, which would be important for optimizing individualized treatment plans to improve prognosis and/or prevent recurrent disease.

The aim of the current study is to apply an exploratory CT-based radiomics analysis to investigate imaging biomarkers of clinical outcomes in SBRT patients from pre-treatment images. This approach could have a large impact for precision medicine, as radiomic biomarkers are non-invasive and can be applied to imaging data that are already acquired in clinical settings.

Materials and methods

Patient characteristics

This study was Institutional Review Board (IRB) approved for analysis of non-small cell lung cancer (NSCLC) patients who underwent stereotactic body radiation therapy (SBRT) treatment at our institution between 2009 and 2014. This was a retrospective study and therefore, IRB approval was obtained for waiver of consent. The patient population was limited to patients with early stage NSCLC (overall stage I–II, N0). Patients that did not have a free breathing computed tomography (CT) scan on file ($n = 10$), had greater than a 1-week duration between CT image acquisition and the start of treatment ($n = 2$), had multiple SBRT treatments and/or multiple tumor lesions ($n = 17$), or received induction chemotherapy ($n = 2$) were excluded from this study. In addition, patients who fulfilled any of the following criteria were also excluded: had metastases to the lung from other sites of primary disease ($n = 30$), locally recurrent disease ($n = 5$), had small cell lung cancer ($n = 1$) or atypical carcinoid ($n = 1$) histology, or were overall stage III or IV ($n = 1$). None of the patients received additional chemotherapy after SBRT. A total of 113 patients were included in the analysis and their characteristics can be found in Table 1.

SBRT treatment and clinical endpoints

All patients were treated with SBRT according to institutional standards. SBRT was restricted to peripheral tumors as defined in Radiation Therapy and Oncology Group (RTOG) 0236 [9] and abdominal compression was used if tumor motion was greater than 1 cm. Treatment planning was performed on 4D CT scans where the internal target volume was defined, and a planning target volume (PTV) with a 5 mm margin with no clinical target volume margin was created. For tumors close to the chest wall, patients received a dose of 10–12 Gy × 5 fractions, and 12–14 Gy × 4 fractions or 18 Gy × 3 fractions for all other tumors. One patient was unable to complete the full course of treatment due to death and only received 1 fraction of 18 Gy (delivered biologically effective dose of 50.4 Gy). Exac Trac, cone-beam CT and portal imaging using a linear accelerator were used for daily setup and image-guided treatment.

Follow-up chest CT scans with contrast (unless the patient had a contraindication to contrast, e.g. renal dysfunction or allergy) were performed every three to six months after treatment based on United States national guidelines [12] to assess tumor progres-