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Research Paper

Impact of experimental design on PET radiomics in predicting somatic mutation status

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ABSTRACT

Purpose: PET-based radiomic features have demonstrated great promises in predicting genetic data. However, various experimental parameters can influence the feature extraction pipeline, and hence, Here, we investigated how experimental settings affect the performance of radiomic features in predicting somatic mutation status in non-small cell lung cancer (NSCLC) patients.

Methods: 348 NSCLC patients with somatic mutation testing and diagnostic PET images were included in our analysis. Radiomic feature extractions were analyzed for varying voxel sizes, filters and bin widths. 66 radiomic features were evaluated. The performance of features in predicting mutations status was assessed using the area under the receiver-operating-characteristic curve (AUC). The influence of experimental parameters on feature predictability was quantified as the relative difference between the minimum and maximum AUC (δ).

Results: The large majority of features (n = 56, 85%) were significantly predictive for EGFR mutation status (AUC ≥ 0.61). 29 radiomic features significantly predicted EGFR mutations and were robust to experimental settings with $\delta_{Overall} < 5\%$. The overall influence ($\delta_{Overall}$) of the voxel size, filter and bin width for all features ranged from 5% to 15%, respectively. For all features, none of the experimental designs was predictive of KRAS + from KRAS− (AUC ≤ 0.56).

Conclusion: The predictability of 29 radiomic features was robust to the choice of experimental settings; however, these settings need to be carefully chosen for all other features. The combined effect of the investigated processing methods could be substantial and must be considered. Optimized settings that will maximize the predictive performance of individual radiomic features should be investigated in the future.

1. Introduction

Functional positron emission tomography imaging with the glucose analog ^{18}F-fluorodoxyglucose (^{18}F-FDG PET) is widely used for diagnosis and staging in oncology. ^{18}F FDG PET plays an increasingly important role in the assessment of treatment response [1] and planning of radiotherapy [2]. Furthermore, ^{18}F FDG PET imaging can capture the different metabolic phenotypes that exist between tumors [3,4]. Quantification of these phenotypes may improve tumor characterization for individualized therapy [4,5]. Radiomics extracts an atlas of features that describe the tumor phenotype from standard of care images through the utilization of advanced mathematical algorithms that quantify the relationship between image voxels [6,7]. Recently, PET radiomic features have demonstrated tremendous promise in predicting clinical outcomes [8,9], treatment response [10,11], and genomic data [3] in various malignancies.

As part of the feature extraction pipeline, PET images undergo two image processing methods [5]. First, the voxel sizes are resampled. Thus far, radiomic studies have relied on retrospective PET imaging data, which are often acquired on different scanners and are reconstructed differently, leading to variability in the voxel size [12,13]. Therefore, for radiomic analysis, many research groups resample the voxel size with an interpolation filter in order to obtain a uniform size across all patients [5,14]. Second, the image intensity of PET images are often discretized (or binned) into a limited range of intensity values to reduce image noise [5] and increase feature computational efficiency [6].

The values and methods chosen for these image processing steps are

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often selected without clear justification or are simply not mentioned in many radiomic studies. Therefore, it is unclear whether these parameters impact the performance of PET radiomic features in predicting outcomes or status and what parameters will maximize the predictability of the features. Researchers have reported that the quantitative value of PET radiomic features is sensitive to the choice of discretization methods [15,16]. However, the effects of the resampled voxel size and interpolation filter on PET feature quantification have not been investigated. Furthermore, the impact of these settings on the ability of radiomic features to predict clinically valuable information has not been reported. With the overall goal of the clinical implementation of radiomics, it is important to study the impact of these parameters on the predictive performance of radiomic features.

Due to the high incidence and recurrence rate of non-small cell lung cancer (NSCLC) [17], there has been considerable interest in applying radiomics to characterize the disease in order to improve prognosis and better tailor treatments for individual patients [4]. Initiation and progression of NSCLC tumors are driven by somatic mutations in key oncogenes (e.g. epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene homolog (KRAS)) [18]. Early prediction of the oncogene mutation status may provide information for individualized therapy for NSCLC patients [18]. PET-based radiomic features have shown to be significantly associated with NSCLC mutation status [3]. Furthermore, unlike prediction of treatment outcomes (e.g. overall survival), the prediction of somatic mutations is not confounded by treatment methods as they are an intrinsic characteristic of the tumor. In this study, we investigated how various experimental settings influence the feature quantification and performance of radiomic features in predicting somatic mutations.

2. Methods and materials

2.1. Patient imaging

This retrospective study was conducted under a Dana-Farber Cancer Institute and Brigham and Women's Hospital Institutional Review Board approved protocol. This study included 348 patients with NSCLC who received diagnostic ^{18}F FDG PET/CT scans prior to treatment between September 2003 and December 2013.

Patients were injected with 348–921 MBq of ^{18}F FDG and PET images were acquired approximately 65 min after injection on a GE Discovery (GE Healthcare, Waukesha, WI), Siemens Biograph (Siemens AG, Erlangen, Germany), or GEMINI TF (Philips Medical Systems, Cleveland, OH) PET/CT scanner (Table 1). PET/CT images of 81, 135, 12, and 46 patients were acquired on the GE-Discovery ST, STE, LS, and RX models, respectively. Forty-three and 9 patients underwent a PET/CT Siemens Biograph mCT and True Point scanner, respectively. However, scanner information of 8 patients was unavailable. Attenuation correction was performed on the PET images using the corresponding CT images. The acquisition time was 3–5 min per bed position for a whole-body scan. Patient characteristics are shown in Table 1.

Tissue samples of primary tumors were acquired through biopsy or surgical resection. Somatic mutations in the EGFR and KRAS oncogenes were tested using PROFILE Oncomap or a polymerase chain reaction (PCR) method. PROFILE Oncomap is a mass spectrometry genotyping technique that analyzes over 470 unique mutations in 41 oncogenes. 49% (170/348) of patients had their mutation status identified by PROFILE Oncomap and 51% (178/348) using PCR. 13% (44/348) patients harbored EGFR mutations, while 28% (96/348) patients had KRAS mutations.

2.2. Experimental settings for PET feature extraction

The impact of the parameters chosen for three image processing steps on the predictive performance of PET radiomic features was investigated. These processing steps, included resampled voxel sizes, interpolation filters and bin widths for image intensity discretization. The parameters for each processing step are listed in Table 2. Each combination of parameters are hereafter referred to as experimental settings.

A region-of-interest was defined for each tumor on the PET image by

Table 1
Patient characteristics. NOS = Not Otherwise Specified. Other = histology includes carcinoid tumor (n = 4), adenosquamous carcinoma (n = 4), sarcomatoid carcinoma (n = 2), undefined non-small cell lung cancer (NSCLC) (n = 3) and mixed NSCLC and SCLC (n = 1).

	KRAS+	EGFR+	Total
Number of Patients	96	44	348
Sex			
Male	34 (35%)	9 (20%)	134 (39%)
Female	63 (65%)	35 (80%)	214 (61%)
Median age (year)	67	61	65
Range	(46–84)	(34–88)	(34–93)
Ethnicity			
Caucasian	91 (95%)	38 (86%)	316 (91%)
African American	4 (4%)	2 (5%)	21 (6%)
Hispanic	1 (1%)	2 (5%)	4 (1%)
Asian	0 (0%)	2 (5%)	6 (2%)
Not reported	0 (0%)	0 (0%)	1 (0%)
Smoking history			
Current/Former	93 (97%)	24 (55%)	286 (82%)
Never	3 (3%)	20 (45%)	62 (18%)
Primary site			
Upper lobe	57 (59%)	28 (64%)	215 (62%)
Middle lobe	12 (13%)	1 (2%)	27 (8%)
Lower lobe	24 (25%)	14 (32%)	98 (28%)
Overlapping lesion	1 (1%)	1 (2%)	2 (1%)
Clinical stage			
I	30 (31%)	15 (34%)	102 (29%)
II	11 (11%)	4 (9%)	44 (13%)
III	36 (38%)	16 (36%)	144 (42%)
IV	19 (20%)	9 (21%)	58 (16%)
Tumor grade			
Well-differentiated	8 (8%)	4 (9%)	32 (9%)
Moderately-differentiated	25 (26%)	19 (43%)	107 (31%)
Poorly-differentiated	36 (38%)	13 (30%)	126 (36%)
Not determined	27 (28%)	8 (18%)	83 (24%)
Histology			
Adenocarcinoma	84 (88%)	36 (82%)	251 (72%)
Squamous cell carcinoma	2 (2%)	0 (0%)	31 (9%)
Non-small cell lung carcinoma NOS	10 (10%)	7 (16%)	60 (17%)
Other	0 (0%)	0 (0%)	7 (2%)
No pathology report available	0 (0%)	1 (2%)	3 (1%)
PET/CT Scanners			
GE Discovery			
ST	21 (22%)	13 (30%)	81 (23%)
STE	36 (37%)	16 (36%)	135 (39%)
LS	3 (3%)	2 (5%)	12 (3%)
RX	13 (14%)	6 (14%)	46 (13%)
Siemens Biograph			
mCT	15 (16%)	5 (11%)	43 (13%)
True Point	3 (3%)	1 (2%)	9 (3%)
Phillips Gemini TF	5 (5%)	0 (0%)	14 (4%)
Not specified	0 (0%)	1 (2%)	8 (2%)

Table 2
Processing steps and their corresponding parameters.

Image Processing Step	Parameters
Voxel sizes	$1 \times 1 \times 1\ mm^3$, $2 \times 2 \times 2\ mm^3$, $3 \times 3 \times 3\ mm^3$, $4 \times 4 \times 4\ mm^3$
Interpolation filters	Nearest-neighbor, Linear, Cubic, Spline
Bin width	0.1, 0.2, 0.3, 0.4, 0.5

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