

## RESEARCH ARTICLE

# Robust radiogenomics approach to the identification of *EGFR* mutations among patients with NSCLC from three different countries using topologically invariant Betti numbers

Kenta Ninomiya<sup>1</sup>, Hidetaka Arimura<sup>2\*</sup>, Wai Yee Chan<sup>3\*</sup>, Kentaro Tanaka<sup>4</sup>, Shinichi Mizuno<sup>5</sup>, Nadia Fareeda Muhammad Gowdh<sup>3</sup>, Nur Adura Yaakup<sup>3</sup>, Chong-Kin Liam<sup>6</sup>, Chee-Shee Chai<sup>7</sup>, Kwan Hoong Ng<sup>3</sup>

**1** Division of Medical Quantum Science, Department of Health Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, **2** Faculty of Medical Sciences, Division of Medical Quantum Science, Department of Health Sciences, Kyushu University, Fukuoka, Japan, **3** Faculty of Medicine, Department of Biomedical Imaging, University of Malaya, Kuala Lumpur, Malaysia, **4** Department of Respiratory Medicine, Kyushu University Hospital, Fukuoka, Japan, **5** Division of Medical Sciences and Technology, Department of Health Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, **6** Faculty of Medicine, Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia, **7** Faculty of Medicine and Health Science, Department of Medicine, University Malaysia Sarawak, Kota Samarahan, Sarawak, Malaysia

\* [arimurah@med.kyushu-u.ac.jp](mailto:arimurah@med.kyushu-u.ac.jp) (HA); [waiyec@ummc.edu.my](mailto:waiyec@ummc.edu.my) (WYC)



## OPEN ACCESS

**Citation:** Ninomiya K, Arimura H, Chan WY, Tanaka K, Mizuno S, Muhammad Gowdh NF, et al. (2021) Robust radiogenomics approach to the identification of *EGFR* mutations among patients with NSCLC from three different countries using topologically invariant Betti numbers. PLoS ONE 16(1): e0244354. <https://doi.org/10.1371/journal.pone.0244354>

**Editor:** Francesco Bianconi, Università degli Studi di Perugia, ITALY

**Received:** September 27, 2020

**Accepted:** December 9, 2020

**Published:** January 11, 2021

**Copyright:** © 2021 Ninomiya et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** All relevant data are within the paper and its [Supporting information files](#).

**Funding:** This study was supported by a grant from Center for Clinical and Translational Research of Kyushu University Hospital and JSPS KAKENHI Grant Number 20K08084. The funders had no role in study design, data collection and analysis,

## Abstract

### Objectives

To propose a novel robust radiogenomics approach to the identification of epidermal growth factor receptor (*EGFR*) mutations among patients with non-small cell lung cancer (NSCLC) using Betti numbers (BNs).

### Materials and methods

Contrast enhanced computed tomography (CT) images of 194 multi-racial NSCLC patients (79 *EGFR* mutants and 115 wildtypes) were collected from three different countries using 5 manufacturers' scanners with a variety of scanning parameters. Ninety-nine cases obtained from the University of Malaya Medical Centre (UMMC) in Malaysia were used for training and validation procedures. Forty-one cases collected from the Kyushu University Hospital (KUH) in Japan and fifty-four cases obtained from The Cancer Imaging Archive (TCIA) in America were used for a test procedure. Radiomic features were obtained from BN maps, which represent topologically invariant heterogeneous characteristics of lung cancer on CT images, by applying histogram- and texture-based feature computations. A BN-based signature was determined using support vector machine (SVM) models with the best combination of features that maximized a robustness index (RI) which defined a higher total area under receiver operating characteristics curves (AUCs) and lower difference of AUCs