CT features of HER2-mutant lung adenocarcinomas

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ABSTRACT

Objectives: To describe the radiological phenotype of HER2-mutant lung cancers on CT at presentation.

Methods: Eligible patients with lung adenocarcinomas with HER2 mutations were stage-matched with two control groups (EGFR- and KRAS-mutant groups). Evaluated CT features of the primary tumor included size, location, consistency, contour, presence of pleural tags and pleural retractions. Presence of pleural effusions, lung metastases, adenopathy, chest wall invasion, and were also recorded. Wilcoxon rank-sum and Fisher’s exact tests were used to compare continuous and categorical features, respectively.

Results: One hundred and fifty-four patients were identified: 50 (33%) harbored HER2 mutations, 56 (36%) harbored KRAS mutations, and 48 (31%) harbored EGFR mutations. Compared with KRAS, HER2 tumors presented as smaller lesions (2.3 cm versus 2.9 cm, \(p = 0.005\) for length; 1.6 cm versus 2.1 cm, \(p = 0.002\) for width) with the presence of pleural tags (74% vs. 52%, \(p = 0.03\)), pleural retractions (58% vs. 39%, \(p = 0.006\)), ipsilateral hilar (36% vs. 16%, \(p = 0.03\)) and scalene/supraclavicular N3 adenopathy (24% vs. 7%, \(p = 0.03\)). Compared with EGFR, pleural retractions were more prevalent among the HER2 tumors (58% vs. 37%, \(p = 0.05\)).

Conclusions: Lung adenocarcinomas with HER2 gene mutation exhibit an aggressive behavior manifesting by higher incidence of local invasion, compared to KRAS and EGFR mutant controls, and a nodal metastatic spread compared to KRAS-mutant control. This is the first radiogenomics study of HER2 mutations in lung cancer.

1. Introduction

Lung cancer remains the leading cause of cancer death worldwide, accounting for 1.69 million deaths in 2015 and approximately 19% of the total cancer death toll according to the World Health Organization [1]. In the United States, the American Cancer Society estimated that 222,500 new cases of lung cancer will be diagnosed in 2017, with an estimated mortality of 70% (155,870 deaths) among both sexes [2]. Of the two main types of lung cancer, non-small cell lung cancer comprises 80 to 85% of lung cancers and histologically, 40% of these are adenocarcinomas [3]. The discovery of the epidermal growth factor receptor gene (EGFR) mutation in patients with lung adenocarcinomas in 2004 [4–6] and the evolution of genomic sequencing and targeted therapy have resulted in the further subclassification of lung adenocarcinomas based on the presence of driver oncogenes.

The human epidermal growth factor receptor 2 gene (HER2/ERBB2) is an important driver oncogene for lung adenocarcinomas. HER2, the protein encoded by this gene, is a tyrosine kinase receptor of the ErbB family. HER2 has no direct activating ligand; it serves as the preferred and most stable hetero-dimerization partner for all the other family receptors, especially EGFR. HER2 dysregulation presents itself as HER2 protein overexpression in 6% to 35% of non-small cell lung cancer, gene amplification in 10% to 20%, and HER2 mutations in 2% to 4% [7, 8], resulting in constitutive activation of intracellular signaling through the PI3K/AKT/mTOR and MEK/ERK pathways, and subsequently promoting cellular mitosis and proliferation [9, 10].

As new drug development for HER2-mutant lung cancers is accelerating, it is increasingly important to study the unique characteristics of this group of patients [7, 11, 12]. Radiogenomics is the study of the radiological appearance of tumors in association with genomic alterations, including driver oncogenes [13]. It is highly promising for the follow-up assessment of tailored targeted therapies. Rizzo et al. has
noted a preponderance for air bronchograms, pleural retractions, small lesion size, and absence of fibrosis for EGFR-mutant lung adenocarcinomas; and a round lesion shape for KRAS-mutant adenocarcinomas in addition to presence of nodules in non-tumor lobes [1-4]. As such the goal of this study was to identify the radiologic characteristics of HER2-mutant lung adenocarcinomas in comparison with other non-small cell lung cancer subtypes, specifically KRAS- and EGFR-mutant lung adenocarcinomas.

2. Materials and methods

2.1. Patient selection

We undertook this retrospective study at our institution, a tertiary cancer referral center. The study was approved by our Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act. Patient informed consent was waived and all data collected for this study were de-identified. We screened our institutional database for consecutive patients with biopsy-proven lung adenocarcinomas of any stage with HER2 mutations seen in the thoracic oncology service between February 9, 2007, and August 17, 2015. All patients had also undergone molecular profiling performed by the Department of Pathology using a number of assays: fragment analysis, Sanger sequencing, Sequenom hotspot testing or broad, hybrid-capture next-generation sequencing (MSK-IMPACT, Illumina HiSeq). Of all potentially eligible HER2 patients, only patients with at least one available pre-biopsy CT scan on our institutional Picture Archiving and Communication System (PACS, GE Centricity RA1000, GE Healthcare, Chicago, IL) were included in the study. Therefore, the final HER2 population for this study consisted of 50 patients. In addition, we searched our database for NSCLC patients with KRAS or EGFR mutations to serve as control groups, since HER2 mutations are generally considered mutually exclusive with these mutations in lung adenocarcinomas. These controls were stage-matched with the HER2 mutation cohort. The final study population consisted of 154 patients. We recorded patient clinical information retrieved from our electronic medical record, such as age, sex, and stage of disease. There was no prior or current treatment for lung cancer in our selected patients.

2.2. Image analysis

The earliest available CT scan before biopsy was selected. Two junior radiologists (P.S. and A.L.) reviewed each CT separately, and then two senior thoracic radiologists (A.P. and M.G.) with post-fellowship experience (4 and 21 years of experience respectively) reviewed each CT scan to establish a consensus read. All readers were blinded to clinical data and molecular features at the time of image analysis. All images were reviewed on our institutional PACS. CT slice thickness varied from 0.625 mm to 2.5 mm in twenty-five patients (16%) and from 3 mm to 5 mm in one hundred and twenty-nine patients (84%). Seventy-four patients (48%) received intravenous contrast. The CT scans were performed on either a 16- or 64-slice CT scanner.

2.2.1. Radiologic features of the primary lung tumor

The size of the primary tumor was measured on lung windows by drawing the longest axis for length and then taking the longest perpendicular distance to determine the width [15]. The primary tumor was classified as central, peripheral or indeterminate. A lesion contacting a central bronchus to the lobar level was identified as central; lesions distal to this level were defined as peripheral; and if the lesion spanned both central and distal locations, it was labeled indeterminate [16]. The consistency of the primary tumor was also characterized as “solid” (density obscuring underlying pulmonary vessels and parenchyma), “ground glass” (increased attenuation of the lung parenchyma without obscuring the underlying pulmonary vessels and parenchyma), “mixed,” or “consolidation.” The contour of the primary tumor was described as either “round/oval” with well-defined smooth margins, “lobulated” with well-defined smooth margins, “spiculated”, or as a “mass-like consolidation.” Finally, additional findings were recorded such as the presence of cavitation, air bronchograms, calcifications (intra-lesional densities ≥ 100 Hounsfield units), necrosis, post-obstructive atelectasis, chest wall invasion, lymphangitic spread, pleural tags (linear centrifugal extensions to the pleura or fissure), and pleural retractions.

2.2.2. Ancillary characteristics

Additional ancillary findings were recorded such as the presence of ipsilateral hilar (N1 stage), mediastinal or scalene/supraclavicular lymphadenopathy (N3 stage) (measuring ≥ 1 cm in short axis, rounded, necrotic, enhancing and with loss of fatty hilum [17]); pleural effusion size and laterality; and lung metastases (satellite versus distant nodules).

2.3. Statistical analysis

HER2 patients were stage-matched (stages IA, IB, IIA, IIB, versus stages IIA and IIB, versus stage IV) with controls carrying KRAS mutations as well as separately with controls carrying EGFR mutations using the greedy method [18]. In the case of ties, the first encountered control was chosen by the algorithm.

The Wilcoxon rank-sum test was used to compare continuous characteristics (age, size) between groups, while Fisher’s exact test was used to assess the associations between categorical features and the different mutant groups. p values of < 0.05 were considered significant.

3. Results

3.1. Patient characteristics

One hundred and fifty-four patients with lung adenocarcinoma were identified: 50 (33%) patients with HER2 mutations, 56 (36%) patients with KRAS mutations, and 48 (31%) patients with sensitizing EGFR mutations. Patients with HER2-mutant lung cancers were predominantly female (n = 36, 72%), with a median age of 61.6 years (range, 37.7–84.4), 50% (n = 25) of whom presented with stage 4 disease. Patients with KRAS-mutant lung cancers were predominantly female (n = 30, 54%), with a median age of 69.6 years (range, 38.6–86.3) and stage 4 disease at time of presentation (n = 27, 48%). Patients with EGFR-mutant lung cancers were predominantly female (n = 34, 71%), with a median age of 67.7 years (range, 37.7–87.0) and stage 4 disease at time of presentation (n = 20, 42%).

Comparisons between the HER2-mutant adenocarcinoma group and control groups showed a statistically significant difference in age (61.6 versus 69.6 years, p = 0.009 compared with the KRAS-mutant group; and 61.6 versus 67.7 years, p = 0.03 compared with the EGFR-mutant group), and approaching significance in predilection for the female sex (72% versus 54%, p = 0.07 compared with the KRAS-mutant group). Detailed findings are listed in Table 1.

3.2. CT scan findings

3.2.1. Radiologic features of HER2-mutant lung cancers

Lung cancers with HER2 mutations were frequently peripheral (n = 35, 70%), solid in consistency (n = 33, 66%), spiculated in contour (n = 27, 54%), and were notable for the presence of pleural tags (n = 37, 74%) and pleural retractions (n = 29, 58%) (Figs. 1 and 2). Less commonly, they showed air bronchograms (n = 17, 34%), demonstrated cavitation (n = 3, 6%), calcification (n = 2, 4%), < 50% necrosis (n = 3, 6%) and post obstructive atelectasis (n = 5, 10%).

Common ancillary findings were lymphadenopathy (mediastinal n = 24, 48%; ipsilateral hilar n = 18, 36%; and N3 adenopathy n = 12, 24%), ipsilateral pleural effusion (n = 10, 20%; Fig. 3) as well as
satellite and distant lung nodules (n = 12, 24% and n = 14, 28%, respectively). Findings are summarized in Table 2.

3.2.2. Comparison with control groups

There was a significant difference between HER2-mutant adenocarcinoma group and the KRAS-mutant control group in terms of the axial length and width of the tumor (2.3 cm versus 2.9 cm, \( p = 0.005 \) for length; 1.6 cm versus 2.1 cm, \( p = 0.002 \) for width), the presence of pleural tags (74% versus 52%, \( p = 0.03 \)), pleural retractions (58% versus 39%, \( p = 0.006 \)), ipsilateral hilar adenopathy (36% versus 16%, \( p = 0.03 \)), and N3 adenopathy (24% versus 7%, \( p = 0.03 \)). In addition, there was a prevalence of pleural retractions in HER2-mutant tumors compared with the EGFR-mutant control group (58% versus 37%, \( p = 0.05 \)). On the other hand, no significant statistical difference between patients with HER2 mutation and KRAS mutation regarding the peripheral location (70% versus 86%, \( p = 0.06 \)) and solid consistency (66% versus 82%; \( p = 0.06 \)) of the primary tumor with these characteristics being exhibited less often in HER2-mutant adenocarcinomas compared with the KRAS control group. Similarly, no significant difference was noted when other features were compared (Table 2).

4. Discussion

HER2 gene dysregulation is a known driver of tumor growth and has been identified in several human malignancies, mainly breast, stomach and lung cancers [19–21]. In lung cancer, cancers harboring HER2 mutations can be aggressive, portending a poor prognosis [9, 22]. Mazières et al. described three major types of HER2 dysregulation in patients with non-small cell lung cancer that may increase oncogenic signaling independent from EGFR and KRAS mutations, and ALK fusions. The most common dysregulation is HER2 protein overexpression (6–35%), followed by HER2 gene amplification (2–5%) and HER2 gene mutation (2–4%) [7, 8]. At the same time, however, these cancers might benefit from existing and emergent therapies targeting HER2, especially when combined with conventional chemotherapy [11]. Novel HER2-targeted drugs are being tested and encouraging activity has been seen [16, 23]. A phase II trial in HER2 exon 20 insertion-containing lung cancers showed single agent activity of dacomitinib, a pan-HER inhibitor that binds irreversibly to HER2, HER1 (EGFR), and HER4 tyrosine kinases receptors [12]. A more recent phase II trial of ado-trastuzumab emtansine was declared positive after demonstrating 44% partial response rate in patients with HER2-mutant lung cancers
Radiologic features of HER2-, KRAS-, and EGFR-mutant lung cancers by computed tomography.

| Median (range in cm) | Wilcoxon rank-sum test p-value | HER2 vs KRAS | HER2 vs EGFR |
|----------------------|--------------------------------|--------------|--------------|
| HER2 (n = 50)        | KRAS (n = 56)                 | EGFR (n = 48) | CRAS vs HER2 | EGFR vs HER2 |
| Mass axial length    |                                |              |              |
| 2.3 (0.4, 8.5)       | 2.9 (0.8, 6.9)                | 3.3 (0.8, 9.2) | 0.005*       | 0.13        |
| Mass axial width     | 1.6 (0.4, 7.8)                | 2.1 (0.8, 5.7) | 2.3 (0.6, 7.8) | 0.002*       | 0.23        |

| n (%)                | Fisher's exact test p value | HER2 vs KRAS | HER2 vs EGFR |
|----------------------|-----------------------------|--------------|--------------|
| Central location     |                             |              |              |
| No                   | 39 (78%)                    | 51 (91%)     | 42 (88%)     | 0.10        | 0.29        |
| Yes                  | 11 (22%)                    | 5 (9%)       | 6 (12%)      |
| Peripheral location  |                             |              |              |
| No                   | 15 (30%)                    | 8 (14%)      | 10 (21%)     | 0.06        | 0.36        |
| Yes                  | 35 (70%)                    | 48 (86%)     | 38 (79%)     |
| Indeterminate location |                            |              |              |
| No                   | 47 (94%)                    | 53 (95%)     | 44 (92%)     | 1.00        | 0.71        |
| Yes                  | 3 (6%)                      | 3 (5%)       | 4 (8%)      |
| Consistency          |                             |              |              |
| Solid                | 33 (66%)                    | 46 (82%)     | 32 (67%)     | 0.06        | 0.72        |
| Mixed solid/ground-glass | 9 (18%)          | 8 (14%)     | 11 (23%)    |
| Consolidation        | 8 (16%)                     | 3 (4%)       | 5 (10%)     |
| Contour              |                             |              |              |
| Round/oval           | 5 (10%)                     | 8 (14%)      | 10 (21%)     | 0.22        | 0.42        |
| Lobulated            | 9 (18%)                     | 10 (18%)     | 9 (19%)      |
| Spiculated           | 27 (54%)                    | 35 (63%)     | 24 (50%)     |
| Mass-like consolidation |                          | 9 (18%)     | 3 (5%)      |
| Caviation            |                             |              |              |
| No                   | 47 (94%)                    | 55 (98%)     | 46 (96%)     | 0.34        | 1.00        |
| Yes                  | 3 (6%)                      | 1 (2%)       | 2 (4%)      |
| Air bronchograms     |                             |              |              |
| No                   | 33 (66%)                    | 51 (91%)     | 37 (77%)     | 0.002*      | 0.27        |
| Yes                  | 17 (34%)                    | 5 (9%)       | 11 (23%)    |
| Calcification        |                             |              |              |
| No                   | 48 (96%)                    | 53 (95%)     | 45 (94%)     | 1.00        | 0.67        |
| Yes                  | 2 (4%)                      | 3 (5%)       | 3 (6%)     |
| Post obstructive atelectasis |                     |              |              |
| No                   | 45 (90%)                    | 53 (95%)     | 44 (92%)     | 0.47        | 1.00        |
| Yes                  | 5 (10%)                     | 3 (5%)       | 2 (8%)      |
| Pleural tags         |                             |              |              |
| No                   | 13 (26%)                    | 27 (48%)     | 20 (42%)     | 0.03*       | 0.13        |
| Yes                  | 37 (74%)                    | 29 (52%)     | 28 (58%)    |
| Pleural retraction   |                             |              |              |
| No                   | 21 (42%)                    | 39 (70%)     | 30 (63%)     | 0.006*      | 0.05        |
| Yes                  | 29 (58%)                    | 17 (39%)     | 18 (37%)    |
| Lymphangitic spread  |                             |              |              |
| No                   | 40 (80%)                    | 51 (91%)     | 44 (92%)     | 0.16        | 0.15        |
| Yes                  | 10 (20%)                    | 5 (9%)       | 4 (8)       |
| Satellite nodules    |                             |              |              |
| No                   | 38 (76%)                    | 40 (71%)     | 35 (73%)     | 0.66        | 0.82        |
| Yes                  | 12 (24%)                    | 16 (29%)     | 13 (27)     |
| Nodules in a different lobe |                     |              |              |
| No                   | 36 (72%)                    | 39 (70%)     | 39 (81%)     | 0.83        | 0.34        |
| Yes                  | 14 (28%)                    | 17 (30%)     | 9 (19)      |
| Necrosis             |                             |              |              |
| None                 | 47 (94%)                    | 53 (95%)     | 45 (94%)     | 0.29        | 1.00        |
| < 50%                | 3 (6)                       | 1 (2)        | 3 (6)       |
| 50-100%              | 0 (0)                       | 2 (3)        |
| Chest wall invasion  |                             |              |              |
| No                   | 50 (100)                    | 55 (98%)     | 48 (100)     | 1.00        | NA          |
| Yes                  | 0 (0)                       | 1 (2)        | 0 (0)       |

| n (%)                | Fisher's exact test p value | HER2 vs KRAS | HER2 vs EGFR |
|----------------------|-----------------------------|--------------|--------------|
| Mediastinal lymph nodes |                             |              |              |
| No                   | 26 (52%)                    | 37 (66%)     | 31 (65%)     | 0.17        | 0.23        |
| Yes                  | 24 (48%)                    | 19 (34%)     | 17 (35%)    |
| Ipsilateral hilar N1 lymph nodes |                     |              |              |
| No                   | 32 (64%)                    | 47 (84%)     | 37 (77%)     | 0.03*       | 0.19        |
| Yes                  | 18 (36%)                    | 9 (16%)      | 11 (23%)    |
| Supraclavicular/scalenal N3 lymph nodes |                     |              |              |
| No                   | 38 (76%)                    | 52 (93%)     | 42 (88%)     | 0.03*       | 0.19        |
| Yes                  | 12 (24%)                    | 4 (7)        | 6 (12)      |
| Effusion ipsilateral |                             |              |              |
| None                 | 40 (80%)                    | 48 (86%)     | 44 (92%)     | 0.51        | 0.14        |
| Small/moderate       | 9 (18%)                     | 8 (14%)      | 3 (6)       |
| Large                | 1 (2)                       | 0 (0)        | 1 (2)       |
| Effusion contralateral |                           |              |              |
| None                 | 49 (98%)                    | 54 (96%)     | 48 (100)     | 1.00        | 1.00        |
| Small/moderate       | 1 (2)                       | 2 (4)        | 0 (0)       |

* Significant at p < 0.05.

Lately, radiogenomics has taken radiology a step beyond its conventional descriptive role. The power to see the genomic characteristics of various tumors plays a pivotal role in engineering an adequate targeted therapy in various cancers including lung adenocarcinoma [25–29], and predicting their response to treatment [32]. To our knowledge, our study is the first to describe the CT characteristics of HER2-mutant lung adenocarcinomas. Several other studies have examined the radiologic characteristics of NSCLCs associated with other driver oncogenes. A similar study conducted by Yano et al. for EGFR-mutant NSCLC found a predilection for solid nature [30] and others found a correlation between the size of the primary tumor, its ground glass component, and the probability of harboring EGFR mutation [31].

In our study, we found that HER2-mutant lung cancers occurred commonly in female patients with an advanced stage at time of diagnosis and in a relatively younger age group. Previously, Mazières et al. [8] obtained comparable epidemiological findings, including a median age of 60 years, a high proportion of women (69%), and a high proportion of stage 4 disease at presentation (50%) were found in HER2-mutant NSCLCs. In addition, they and others noted similar observations regarding the predilection of patients with HER2-mutant lung cancers to present in younger females with predominantly stage 4 disease at the time of diagnosis, in addition to a history of minimal to no tobacco exposure [8, 32, 33].

Radiologically, our study also showed that HER2-mutant tumors were significantly associated with a preference for peripheral location, solid consistency, and spiculated contour. When HER2-mutant tumors were compared with the KRAS-mutant control group, they were significantly smaller in size, associated with pleural retractions, more frequent air bronchograms, and a prevalence of pleural tags. In addition, more local (ipsilateral hilar, N1 level) and N3 adenopathy were found with HER2-mutant tumors versus the KRAS-mutant control group.

The preponderance of pleural tags and retractions in HER2-mutant adenocarcinoma might point toward its locally-invasive nature. Furthermore, the more frequent nodal involvement might also point toward the aggressive behavior and early nodal spread of these tumors. In fact, a plausible analogy can be drawn with inflammatory breast cancer which exhibits HER2 amplification in approximately 40% of cases [34], and which tends to pursue an aggressive course with lymphangitic spread, pleural disease, and local invasion. A meta-analysis...
conducted by Elias et al. regarding the various radiologic characteristics of HER2-positive breast cancers shows the strong association between HER2 overexpression and indistinct masses with irregular margins on mammography, ultrasound, and magnetic resonance imaging [25].

The major limitations of our study are the relatively small sample size and its retrospective nature. Because of the low incidence of these genomic events, larger multicenter trials will be required to better describe and consolidate these radiological findings. Moreover, due to the relatively small sample size and the limited pool of controls, we did not adjust for multiple testing due to the exploratory nature of the study; therefore, results should be interpreted with caution, and validation is needed in future studies. In addition, the prevalence of an advanced stage at time of diagnosis (stage 4) for the HER2-mutant and control groups might represent a confounding factor due to lead time bias, since with advanced stage, different radiological features may overlap and co-exist irrespective of the oncogene. By stage-matching the patients, we tried to diminish such possible effects. On another note, the studied CT scans show a varying slice thickness from 0.625 mm to 5 mm, so that lack of thin slices in some scans might have limited evaluation of tumor features. Finally, the wide array of HER2 mutation subtypes might represent an intrinsic heterogeneity factor in our studied group; an interesting area for future studies is to delve into the most common and significant molecular dysregulations of the HER2 oncogene such as exon 20 insertion YVMA [16].

In conclusion, lung adenocarcinomas harboring HER2 mutation display several radiological features that may highlight the aggressive behavior of the primary tumor and its nodal metastatic spread. Moreover, it shares many of its epidemiological and radiographic characteristics with adenocarcinomas harboring other mutations (such as those involving KRAS and EGFR). The continuous advances in molecular and genomic sequencing, in addition to the growing field of radiogenomics, may play a pivotal role in the future characterization of these tumors radiologically.

Conflict of interest

None.

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