Non-invasive tumor genotyping using radiogenomic biomarkers, a systematic review and oncology-wide pathway analysis

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ABSTRACT

With targeted treatments playing an increasing role in oncology, the need arises for fast non-invasive genotyping in clinical practice. Radiogenomics is a rapidly evolving field of research aimed at identifying imaging biomarkers useful for non-invasive genotyping. Radiogenomic genotyping has the advantage that it can capture tumor heterogeneity, can be performed repeatedly for treatment monitoring, and can be performed in malignancies for which biopsy is not available. In this systematic review of 187 included articles, we compiled a database of radiogenomic associations and unraveled networks of imaging groups and gene pathways oncology-wide. Results indicated that ill-defined tumor margins and tumor heterogeneity can potentially be used as imaging biomarkers for 1p/19q codeletion in glioma, relevant for prognosis and disease profiling. In non-small cell lung cancer, FDG-PET uptake and CT-ground-glass-opacity features were associated with treatment-informing traits including EGFR-mutations and ALK-rearrangements. Oncology-wide gene pathway analysis revealed an association between contrast enhancement (imaging) and the targetable VEGF-signalling pathway. Although the need of independent validation remains a concern, radiogenomic biomarkers showed potential for prognosis prediction and targeted treatment selection. Quantitative imaging enhanced the potential of multiparametric radiogenomic models. A wealth of data has been compiled for guiding future research towards robust non-invasive genomic profiling.

INTRODUCTION

Considerable progress had been made in developing targeted therapies for genomic subtypes in cancer, but patient selection for these therapies can be challenging. Radiogenomics (sometimes imaging genomics) is a new, rapidly evolving field of research aimed at developing tools for non-invasive genotyping by identifying imaging biomarkers for genomic subtypes [1–3]. Radiogenomic analysis refers to the integration of radiophenotypes and genomic data in order to find radiogenomic associations (Figure 1). Radiogenomic analysis can be performed using
qualitative- or quantitative (computer-extracted, radiomics) imaging features, which can be used as individual biomarkers or can be incorporated in multiparametric prediction models.

Radiogenomics yields considerable advantages for genotyping. Firstly, tumor genetic heterogeneity can be captured using radiogenomics. Biopsy-based genotyping in the clinical setting is generally confined to a single sample, although multiregional genotyping has been performed effectively to capture tumor heterogeneity [4–6]. Radiogenomic biomarkers have shown a great potential for capturing tumor heterogeneity non-invasively [7, 8]. Secondly, a non-invasive method can be performed repeatedly, and is therefore eminently suitable for treatment follow-up. In addition, radiogenomic markers are important for tumors for which biopsy is unavailable (e.g. glioma, retinoblastoma) [9]. Finally, radiogenomics is fast and cost-effective, generally using routine clinical imaging. Several non-systematic reviews were published on radiogenomics [2, 3, 10–19]. The main purpose of this systematic review was to provide a comprehensive oncology-wide database of radiogenomic associations, and to review their clinical usefulness. A secondary objective was to assess radiogenomics on a pathway-level instead of a gene-level; to perform oncology-wide gene pathway analysis in order to identify relations between imaging and oncopathways.

RESULTS

Database of imaging-genomics associations

We included 187 articles published between July 2004 and February 2017. A PRISMA flow diagram for the inclusion process is available in the Supplementary Table 1. Figure 2 illustrates the exponential growth of publications on a year-over-year basis. The major groups reflected diffuse glioma (n = 79, 42%), non-small cell lung cancer (NSCLC) (n = 51, 27%), and breast cancer (n = 18, 10%). Often, studies used multiple modalities; 105 studies used MRI (56%), 80 CT (43%), 44 FDG-PET (24%), and 5 mammography (3%). In 59/187(32%) articles biological clarifications for imaging-genomics relations were identified. The 2440 identified radiogenomic associations in the database are presented as a pivot table, which provides an easy graphical interface to perform data queries using Microsoft Excel (2010/2013) (Supplementary Table 2). Study characteristics and quality assessment are available in the Supplementary Table 3. The results section focuses on repeatedly identified imaging-genomics associations with possible clinical application.

Glioma: IDH-mutation status and 1p/19q codeletion

The 2016 World Health Organisation (WHO) Central Nervous System (CNS) tumor classification uses a combined phenotypic (histology) and genotypic classification for diffuse glioma (diffuse astrocytic and oligodendrogial tumors grade II-IV) [20]. The major genetic traits are IDH mutation and 1p/19q codeletion, both associated with a more favourable prognosis [21–26]. Table 1 summarizes radiogenomics for IDH-status in glioblastoma (GBM, grade IV glioma), while Table 2 and Supplementary Table 4 show radiogenomics results for IDH-status and 1p/19q codeletion in grade II-III glioma. On MRI, IDH-mutated cases were characterised by increased perfusion parameters in both glioblastoma (higher tumor blood flow) [27] and grade II glioma (higher relative cerebral blood volume) [28]. Additionally, detection of 2-hydroxyglutarate (2-HG) with MR-spectroscopy (MRS) was a strong predictor of IDH-mutations in glioblastoma (grade IV) [29], grade II-III glioma [30] and grade II-III-IV glioma.
Furthermore, four studies applied multiparametric models predicting IDH-status based on qualitative and quantitative features (Supplementary Table 5) [32–35]. 1p/19q codeletion, a pathognomonic trait that defines a distinct glioma entity (oligodendroglioma), was associated with ill-defined tumor borders [36–39] and tumor heterogeneity [36–39] on MRI of grade II-III glioma. Results of one study revealed combined perfusion and MRS metabolite ratios can discriminate tumors with 1p/19q loss of heterozygosity with an accuracy of 72% [40]. MGMT-methylations status is relevant for glioblastoma, as it could aid patient selection for adjuvant temozolomide chemotherapy [41–43]. Supplementary Table 6 summarizes findings of studies assessing MGMT-methylation status [27, 32, 44–52] in glioblastoma. MGMT-methylated tumors showed higher apparent diffusion coefficient (ADC) values on diffusion weighted-MRI (DW-MRI) in four out of five studies [27, 44–47]. Supplementary Table 7 summarizes the findings of studies correlating MR features with EGFR-status in diffuse glioma. MR perfusion parameters correlated with EGFR-amplification [53], and EGFR-mutation status in glioblastoma [54, 55] and with EGFR-expression in grade II-II oligodendroglioma [56] and grade III-IV glioma [57].

**Multiparametric modelling for radiogenomics in diffuse glioma**

Supplementary Table 5 summarizes findings of studies incorporating quantitative imaging and genomics data in multiparametric models. Seven studies created prognostic models using whole-genome data and imaging [58–65]. Four studies successfully correlated quantitative perfusion traits with angiogenic gene signatures [66–69].

**Non-small cell lung carcinoma: EGFR-mutations, ALK-rearrangements, KRAS-mutations**

Radiogenomic studies for NSCLC follow the emerging field of personalized, genotype-directed therapy for NSCLC (Supplementary Table 8). However, divergent findings were reported on the association between presence of EGFR-mutation (treatable with tyrosine kinase inhibitors, TKI) and imaging (standardized uptake value [SUV] on FDG-PET and proportion ground glass opacity [GGO] on CT). FDG-PET uptake was both negatively [70–77] and positively [78, 79] correlated with EGFR-mutations, while other studies found no correlation [74, 80–83]. Additionally, EGFR-mutated tumors were on average more solid (less GGO) [80, 84, 85], although not completely solid (some degree of GGO) [86–88]. However, one study showed an inverse relation [83] and other studies found no association [70, 78, 89–95]. Similarly, ALK-rearranged tumors (treatable with ALK-inhibitors) were more solid in two [95, 96] out of four [80, 85, 95, 96] studies compared with ALK-wild-type (wt) tumors. When using GGO to discriminate ALK-rearrangements from EGFR-mutations, ALK-rearranged tumors were more solid [80, 95]. Compared with ALK-wt, ALK-rearranged tumors had more spiculated [80] and lobulated [95] tumor margins on
Another driver mutation is KRAS, which is the most frequent driver mutation, but no CT or PET features were repeatedly associated with KRAS-mutation status (Supplementary Table 9).

Quantitative imaging and multiparametric modeling for radiogenomics in lung cancer

Recent studies performed multiparametric modelling and quantitative imaging in NSCLC [97–104]. Individual quantitative texture features successfully identified EGFR-mutation (multiple comparisons) [103, 104], as did multiparametric models adopting quantitative (AUC = 0.74–0.91), qualitative, (AUC = 0.89) [87], or combined quantitative-clinical features (AUC = 0.70) [98]. Quantitative CT- and PET-features could also predict ALK or ROS1/RET fusions (sens = 0.73, spec = 0.70) [105]. For development of prognostic imaging biomarkers, two groups used quantitative imaging for predicting prognosis-related gene clusters and found a lower kurtosis value linked with poorer survival [99]. Additionally, a module of tumor size, edge shape, and sharpness could predict survival [97]. Similarly, the prognostic value of PET-imaging was explained from a genomic perspective using radiogenomic analysis [100, 101].

Breast cancer

This review only included studies with analyses on a genomic level; imaging-receptor associations based on

Table 1: Overview of radiogenomics for predicting IDH mutation status in glioblastoma (grade IV), p-values for associations

| Glioma grade | Author      | Year of pub. | N   | MR Necrosis | MR CE Necrosis | MR CE Enhance. | MR ADC Sir.  | MR TBF | MRS (magnetic resonance spectroscopy) | MR Edema | MR Nonenhanced tumour |
|--------------|-------------|--------------|-----|-------------|----------------|----------------|--------------|--------|-------------------------------------|-----------|------------------------|
| Grade IV     | Choi [161]  | 2012         | 29  |             |                |                |              |         |                                     | <0.001    |                        |
|              | Gutman [192]| 2013         | 75  | 0.19        |                | 0.08           |              |         |                                     | 0.6       | 0.23                   |
|              | Wang [200]  | 2015         | 280 |             |                |               | 0.621         |        |                                     | 0.395     |                        |
|              | Yamashita   | 2016         | 55  | <0.05       |                |                |              | >0.05  |                                     | <0.001    |                        |

Table 2: Overview of radiogenomics for predicting IDH mutation status in glioma grade II–III, p-values for associations

| Glioma grade | Author      | Year of pub. | N   | MR Tumour volume | MR Tumour margin | MR Location features | CT Calcifications | MR Heterogeneity | MR CE Enhance. | MR CBV | MRS (magnetic resonance spectroscopy) | MRS (magnetic resonance spectroscopy) | PET | PET FDG | PET SUV | PET max ratio |
|--------------|-------------|--------------|-----|------------------|------------------|----------------------|-------------------|------------------|----------------|--------|-------------------------------------|-------------------------------------|-----|----------|----------|---------------|
| Grade II     | Yu [201]    | 2017         | 92  |                  |                  |                      |                   |                  |                |        |                                     |                                     |     |          |          |               |
|              | Kickingeder | 2015         | 73  |                  |                  |                      |                   |                  |                |        |                                     |                                     |     |          |          |               |
|              | Wang [202]  | 2015         | 146 | <0.05            |                  |                      |                   |                  |                |        |                                     |                                     |     |          |          |               |
| Grade II, III| Metellus    | 2010         | 47  | 0.047            | 0.007            | 0.004                |                   | 0.82             | 0.99           |        |                                     |                                     |     |          |          |               |
|              | Pope [30]   | 2012         | 24  |                  |                  |                      |                   |                  |                |        |                                     |                                     |     |          |          |               |
|              | Saito [205] | 2016         | 250 |                  |                  |                      |                   |                  |                |        |                                     |                                     |     |          |          |               |
| Grade II, III, IV | Nakae   | 2016         | 167 |                  |                  |                      |                   |                  |                |        |                                     |                                     |     |          |          |               |
|              | Kalinina    | 2012         | 75  |                  |                  |                      |                   |                  |                |        |                                     |                                     |     |          |          |               |
immunohistochemistry analysis were reviewed elsewhere [10]. High FDG-PET uptake was found for gene expression signatures for basal-like, while low uptake was found for luminal like cases [106]. Low FDG-PET uptake was also associated with expression of oestrogen-receptor related genes [107]. Other studies associated luminal B genes with quantitative dynamic MRI-perfusion [108] and BRCA-mutations with sharp margins and rim enhancement on MRI [109], but these findings were not independently validated.

**Multiparametric modeling for radiogenomics in breast cancer**

Radiogenomic imaging models were used in breast cancer in twelve studies [110–121]. Five studies [110, 112, 118, 120, 121] focussed on Oncotype Dx gene-expression score, which predicts recurrence in early-stage ER+/HER2- invasive cancers [122]. One [118] additionally assessed prognostic gene assays MammaPrint [123] and PAM50 [124, 125]. Enhancement heterogeneity, on either quantitative perfusion [110, 120] or quantitative texture analysis [118], was associated with high-risk assays in three studies. Rapid contrast uptake predicted high-risk Oncotype Dx in two studies [110, 112]. To increase insight into underlying genomics of MR-perfusion parameters a study associated gene expression profiles with a heterogeneous centripetal perfusion phenotype [116] and another study associated perfusion parameters with regulatory non-coding transcripts of RNA associated with early metastasis [126]. Radiogenomics was applied for monitoring of anti-VEGF treatment by measuring pre- and post-treatment perfusion and associated differential gene expression [119]. Additionally, a qualitative imaging model including tumor heterogeneity and enhancement predicted expression of immune-response genes [114]. Combined analysis of tumor shape (lobulated oval) on mammography and MRI showed significant correlations with Oncotype Dx [121].

**Colorectal cancer**

Nine studies were included for CRC [127–135]. Higher FDG-PET uptake was found for KRAS-mutated tumors in five [128, 129, 133, 136, 137] out of six [134] studies. Additionally, KRAS-mutations could be predicted in a multiparametric model using high FDG-PET uptake in addition to CT texture and perfusion features [137]. Cases that were both KRAS- and TP53-mutated also showed a higher SUVmax [129], as did cases that belonged to the group “KRAS- or BRAF-mutated” [132].

**Renal cell carcinoma**

Eight studies were included for RCC [138–145]. BAP1-mutations, associated with invasive disease [146, 147], showed more calcifications (CT) in two studies, although in one non-significantly (p = 0.09 [138]; p < 0.001 [140]). A radiogenomic risk score, based on a multiparametric qualitative CT model successfully predicted a predefined prognostic gene signature in RCC [142, 143]. One study identified genetic underpinnings of an imaging-based complication prediction score (PADUA) [145].

**Hepatocellular carcinoma**

Three studies were included for HCC [148–150]. Tumors with ill-defined margins on CT showed high expression of a gene expression signature for doxorubicin-sensitivity [150]. Additionally, targetable high VEGF-expression [151] was related to attenuation, heterogeneity and tumor margins on CT [148]. A gene signature of microvenous invasion (indicating poor prognosis) can be predicted by a CT biomarker including presence of small intratumoral internal arteries and the absence of hypodense halos [148]. A different genomic score for venous invasion was correlated with CT intratumoral arteries and margins [150].

**Radiogenomics in other malignancies**

In paraganglioma, four studies found higher PET SUV-values for SDHx-mutated tumors [152–154] or SDHx and VHL-mutated tumors [155], relevant for heritability risk assessment. In head neck tumors, EGFR-expression was related to CT invasion, mass effect, size/volume [156] and lower capillary permeability on perfusion CT [157]. Additionally, 14 studies each reported on radiogenomic associations of 14 other malignancies, respectively (Table 3).

**Oncology-wide comparison of radiogenomic correlations and gene pathway analysis**

Looking at the molecular pathway-level, gene ontology analysis reveals associations between imaging groups and gene pathways in cancer (KEGG) oncology-wide (Table 4). Distinct cancer pathways were associated with imaging group of necrosis (55 genes/6 pathways) and of contrast enhancement (37 genes/6 pathways). Enhancement features (degree) were associated with the targetable signalling pathways of VEGF (p < 0.0001) and PI3K-Akt (p < 0.0001) (Figure 3). In addition, enhancement was associated with mTOR signalling (p < 0.0001), MAPK (p = 0.0004) signalling, Focal adhesion (p < 0.0001) and Apoptosis (p = 0.0069). Necrosis was associated with PI3K-Akt signalling (p = 0.0005) (Figure 3), MAPK signalling (p = 0.0233), Wnt signalling (p = 0.0054), and p53 signalling (p = 0.0348). Furthermore, necrosis was significantly associated with Cell cycle (p < 0.0001) and Focal adhesion (p = 0.0470).

Supplementary Table 10 summarizes associations of imaging and individual genomic features that were found in multiple cancer types. Imaging groups (N = 14) comprised
Table 3: Radiogenomics in other malignancies

| Diagnosis                                      | Study            | Year | N   | Study design (radiogenomic analysis)                                                                 | Genetic feature                                                                 | Significantly correlated imaging feature                                      | p-value  |
|------------------------------------------------|------------------|------|-----|----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------|
| Cervical cancer                                | Halle [194]      | 2012 | 187 | Prediction of expression of a set of hypoxia-induced genes with a DCE-MRI imaging model            | Hyoxia-induced genes set (31)                                                  | DCE-MRI imaging feature model (Abrix)                                         | Multiple significant finding, appendix S2 |
| Diffuse large B-cell lymphoma                  | Lanic [232]      | 2011 | 57  | Multiparametric modelling incorporating imaging (PET) and genomics to predict prognosis            | Germinal center B cell-like (GCB) vs Activated B cell-Like (ABC) (gene set expression) | PET High SUV-uptake                                                          | 0.0291   |
| Extraskelatal myxoid chondrosarcoma            | Tateishi [233]   | 2005 | 19  | Describing MR findings in 19 extraskelatal myxoid chondrosarcoma patients                         | EWS-CHN translocation vs other cytogenic variants                             | MR Peripherial enhancement                                                    | <0.05    |
| Lipoma and atypical lipomatous tumor/ well-differentiated liposarcoma | Brisson [234]   | 2012 | 87  | Identification of CT imaging biomarkers for MDM2 amplifications  (classified as atypical lipomatous tumor/well-differentiated liposarcoma) | MDM2 amplification                                                          | CT Lesion size >10 cm                                                        | 0.011    |
| Melanoma brain metastases                      | Bordia [235]     | 2016 | 98  | Identification of MR imaging features of melanoma brain metastasis associated with genetic profiles and survival | B Raf mutation                                                                  | CT Location: lower limb                                                      | 0.007    |
| Multiple myeloma                               | Mai [236]        | 2016 | 164 | Identification of genetic underpinnings of qualitative MR imaging patterns                        | Any adverse cytogenetics (chrom. 17p deletion/4;14;1q amplification)           | CT Solid fat content                                                          | 0.002    |
| Ovarian cancer (high grade serous)            | Vargas [237]     | 2015 | 46  | Qualitative and quantitative assessment of CT features to predict gene expression subtypes (Clovar) | Mesenchymal gene expression subtype (Clovar)                                    | MR Diffuse patterns                                                          | 0.02     |
| Neuroblastoma                                  | Liu [238]        | 2015 | 42  | Use of FDG-PET and FDOPA-PET for distinguishing neuroblastoma genomic subtypes                     | CF2 expression                                                                  | CT Mesentric infiltration                                                     | 0.0002   |
| Medulloblastoma                                 | Perreault [239]  | 2014 | 47  | Qualitative assessment of MR imaging features to predict 4 molecular subgroups (wingless, sonic hedgehog, group 3, and group 4) | Wingless                                                                        | CT Diffuse peritoneal involvement                                             | 0.004–0.012 |
| Pilocytic astrocytoma                          | Zakrzewski       | 2015 | 86  | Identification of transcriptional profiles related to radiological findings                      | Transcriptional profiles                                                       | MR: Solid or mainly solid, Cystic/Enhanced, Cystic/Non enhanced, Largely necrotic | No relation found |
| Pancreatic cancer                              | Shi [131]        | 2015 | 60  | Correlation of PET-imaging features with major oncogenic alternations                            | CDKN2A loss of heterozygosity                                                  | PET (MTV and TLG)                                                            | 0.029–0.021 resp. |
| Prostate cancer                                | Stoyanova [240]  | 2016 | 6   | Multiparametric quantitative imaging association with whole genomem (gene ontology)            | Whole genome expression, predefined genomic classifiers                        | Multiple quantitative imaging features including DCE-MRI                      | Significant findings for both predefined gene classifiers as newly identified pathways |
| Thyroid cancer                                 | Nagarajah [241]  | 2015 | 81  | Identification of PET-imaging features related to BRAFe600E mutation                           | BRAFe600E mutation                                                            | PET SUVmax                                                                    | 0.019    |

**DISCUSSION**

This study provided a comprehensive database of imaging-genomics associations, in which queries can be made (Supplementary Table 2). This review focussed on features (e.g. tumor size, multifocality) of both MRI and CT in various malignancies. Results included the correlations of enhancement features with *VEGF*-expression in brain tumors (glioblastoma) [158] and head-neck tumors (oral cavity SCC) [156].
both imaging-genomics associations with possible clinical application per cancer subtype and oncology-wide patterns in radiophenotype-genotype relations.

**Diffuse glioma**

The 2016 WHO classification for diffuse glioma in adults is largely based on IDH1-mutation status and 1p/19q codeletion [159]. However, biopsy-based genotyping is an invasive technique that can be unreliable due to spatial tumor heterogeneity. Imaging biomarkers reflect the whole tumor and could possibly enhance genotyping accuracy non-invasively. Compared to IDH-wild type, IDH-1/2 mutated glioma have a favourable prognosis [21–23, 160]. IDH-status is the top-level diagnostic stratification after histology in the WHO index 2016 [159]. Although 12 out of 15 studies identified associations between imaging and IDH-status, the majority of findings were not independently validated. MR-perfusion [27, 28] and 2-HG MR-spectroscopy parameters [30, 31, 161], however, were correlated with IDH-status in multiple studies and yield potential for future imaging-based IDH-mutation detection. The oncometabolite 2-HG is elevated in IDH-mutated cases and can be depicted using MR-spectroscopy [29, 162–164], although this is technically challenging due to overlap of neighbouring metabolites (GABA, glutamate and glutamine) in the spectrum. State-of-the-art MR systems generate the high-quality spectra needed for 2-HG detection, enabling clinical practice integration [165]. The codeletion of chromosome 1p19q is an early genetic event in development of oligodendroglioma associated with greater chemosensitivity and improved survival [24–26, 159]. 1p19q co-deleted tumors were repeatedly characterised as heterogeneous [36–39] with ill-defined margins [36–39]. This phenotype is possibly caused by enhanced invasiveness of 1p19q co-deleted glioma. MGMT-methylated glioblastoma respond better to DNA alkylating chemotherapy with improved prognosis [41, 42]. The finding that MGMT-methylated cases showed higher ADC-values on DWI-MRI [27, 44–47] may only be relevant for detecting non-methylated, bad-responding elderly patients who may decide to refrain from treatment [166, 167]. EGFR aberrations were often correlated with MR-perfusion parameters, possibly due to the effect of EGFR on cell invasiveness and angiogenesis. However, despite the important role of EGFR in glioma development

| Imaging group | Genes in input (n) | Genes from input available in pathway (n) | Genes in pathway annotation (n) | KEGG cancer pathway | p-value | p Bonferroni corrected |
|--------------|------------------|---------------------------------|---------------------------------|---------------------|---------|-----------------------|
| necrosis degree | 55 | 9 | 124 | Cell cycle | <0.0001 | <0.0001 |
| necrosis degree | 55 | 10 | 346 | PI3K-Akt signalling pathway | 0.0000 | 0.0005 |
| necrosis degree | 55 | 6 | 139 | Wnt signalling pathway | 0.0000 | 0.0054 |
| necrosis degree | 55 | 7 | 259 | MAPK signalling pathway | 0.0002 | 0.0233 |
| necrosis degree | 55 | 4 | 68 | p53 signalling pathway | 0.0003 | 0.0348 |
| necrosis degree | 55 | 6 | 206 | Focal adhesion | 0.0004 | 0.0470 |
| enhancement degree | 37 | 12 | 346 | PI3K-Akt signalling pathway | <0.0001 | <0.0001 |
| enhancement degree | 37 | 8 | 206 | Focal adhesion | <0.0001 | <0.0001 |
| enhancement degree | 37 | 5 | 60 | mTOR signalling pathway | <0.0001 | <0.0001 |
| enhancement degree | 37 | 5 | 61 | VEGF signalling pathway | <0.0001 | <0.0001 |
| enhancement degree | 37 | 7 | 259 | MAPK signalling pathway | 0.0000 | 0.0004 |
| enhancement degree | 37 | 4 | 86 | Apoptosis | 0.0001 | 0.0069 |

*a*We excluded enhancement pattern features. *b*We required a minimal of 20 genes of radiogenomic associations for an imaging feature group (genes from input) for inclusion in analysis.
[168], suitable EGFR-targeted therapies for glioma have not been developed [169]. To ensure standardised glioma imaging features, models increasingly adopt quantitative imaging. Models allow for incorporating multidimensional parameters. Machine learning techniques are successfully adopted to optimize feature selection [34, 170, 171]. Potentially applicable models were found using quantitative features (3D texture, shape) [62], and a combination of quantitative and qualitative features (volume, haemorrhage, T1/FLAIR ratio) [59], both stratifying for survival and unique pathway activity. Additionally, prognostic models using quantitative imaging recently entered the phase of being tested in prospective setting [69, 171]. Although quantitative radiogenomic analyses showed great potential for genotyping in glioma, the vast variety of features and study designs made comparing results challenging.

**Non-small cell lung cancer**

Since specific therapies are available for genomic subgroups of NSCLC, genotyping is important for directing therapy [172]. However, biopsy-based genotyping can cause treatment delay [173]. Radiogenomics may provide a reliable non-invasive tool for fast genotyping. EGFR-mutated [174, 175] and ALK-rearranged [172, 176, 177] tumors are targetable and are therefore extensively researched in radiogenomics. Repeatedly, FDG-PET was associated with EGFR-mutations, which may be biologically explained by the activating role of mutated EGFR glycolysis through AKT-signalling [178, 179]. The major studies showed a higher FDG-PET uptake for EGFR-mutated tumors; one of these validated their results in an independent cohort [73]. The three studies that found a lower uptake for EGFR-mutated cases were possibly unreliable because lower uptake was either not confirmed in multivariate analysis [76], found in metastasis only [75], or found because the comparison group had highly avid KRAS-cases [77]. Proportion GGO versus solid appearance on CT might be useful to differentiate genetic NSCLC-subtypes. Seemingly, wild type tumors have a large proportion GGO, EGFR-mutated tumors have a small component GGO, and ALK-rearranged tumors are the most solid. However, validation studies with standardised GGO measurements are needed to reliably discriminate genotypes. Similarly, standardised tumor morphology features need to be assessed in order to validate the predictive value of ill-defined tumor borders for ALK-status. Multiparametric (quantitative imaging) studies can be powerful for predicting individual genetic traits, as well as gene clusters related to prognosis. However, findings need to be validated in independent cohorts before they can be used in clinical practice.

![Figure 3: Genetic traits associated with either enhancement or necrosis.](image)

Genes associated with degree of enhancement ($N = 37$) and genes associated with necrosis ($N = 55$) are depicted. The genes IDH1, NF1, TP53, PGF and EGFR are shared between both groups. The two gene sets were both enriched for PI3K-Akt signalling (enhancement: 12 common genes, Bonferroni corrected $p < 0.0001$; necrosis: 10 common genes, Bonferroni corrected $p = 0.0005$).
Breast cancer

In breast cancer, most radiogenomic associations were not independently validated. Limited results indicate FDG-PET can possibly discriminate molecular subtypes [106, 107]. Gene-expression scores such as Oncotype Dx recurrence risk test and MammaPrint metastasis risk test become increasingly important for clinical decision making in breast cancer, especially to prevent unnecessary chemotherapy. Since genetic tests are costly and time-consuming, studies aimed at finding imaging surrogates. In multiple studies perfusion features showed potential for predicting high-risk genetic tests, indicating tumor perfusion may be sign of poor prognosis in breast cancer. Studies furthermore indicated the potential of perfusion imaging for predicting gene expression markers for anti-VEGF treatment response. However, clinically applicable models are yet to be established.

Colorectal carcinoma, renal cell carcinoma, hepatocellular carcinoma

In colorectal carcinoma, KRAS-mutation indicates irresponsiveness to EGFR-targeted treatment [180, 181] and showed high FDG-PET uptake in multiple studies. The lack of this association in one study [134] and a reported low accuracy for prediction [129] might be explained by false-positive high uptake due to inflammation [136]. Although findings are not yet prospectively validated, FDG-PET has great potential for providing biomarkers for EGFR-treatment decision making in CRC. In renal cell carcinoma, the amount of calcifications shows potential for predicting BAP1-status, which could be useful for assessing stage, grade and invasiveness [146, 147]. However, findings need validation. Although multiparametric modelling studies in RCC were limited, great strides are put in assessing its application for predicting prognosis- and complication risk [142, 143, 145]. For hepatocellular carcinoma, radiogenomic biomarkers could aid both treatment selection (VEGF-targeted and doxorubicin treatment) as well as prognosis prediction. Microscopic venous invasion, a sign of poor prognosis and high recurrence risk, was associated with small intratumoral arteries (CT), which was independently validated [182]. However, it was noticed patients were not selected indiscriminately [183]. The amount of studies and their population size were too low to draw conclusions.

Patterns in radiogenomic associations

Repeatedly found imaging-genomics associations show patterns among different neoplasms. A convincing relation was found for enhancement on imaging and VEGF-expression, identified in brain and head neck cancers. The same association was found in a study (not included) assessing radiogenetics using immunohistochemistry in HCC [184]. For a more profound understanding of radiogenomic relations and underlying regulatory networks, insights into the related biological process can be of considerable value. Angiogenesis was the most mentioned biologic link between imaging and genomics in glioblastoma [48, 54, 55, 57, 66, 67, 158], oligodendroglioma [56, 185], breast cancer [102, 126], oral cavity SCC [156], and RCC [138]. Angiogenesis-related genes such as VEGF and EGFR genes were compared with angiogenesis related imaging features such as perfusion and contrast enhancement. Similarly in gene pathway analysis, angiogenesis (biology) may be the link between enhancement (imaging) and VEGF-pathway-signalling (genomics).

Oncology-wide gene pathway analysis of radiogenomic associations

The importance of targeting multiple regulators in cancer pathways instead of single genes, is increasingly recognized. Genes associated with enhancement were enriched for the VEGF-signalling pathway. Similar to the association between contrast enhancement and the VEGF gene, enhancement may be associated with the VEGF signalling pathway due to its regulating role in angiogenesis. Imaging biomarkers for the VEGF pathway may have clinical implications as they could aid patient selection for VEGF-targeted treatment. VEGF-targeted therapy has been shown to be effective in various cancer types, including CRC, NSCLC, and breast cancer [186, 187].

Gene pathway analysis results indicated furthermore that contrast enhancement and necrosis detected with imaging reflect MAPK- and PI3K-Akt-mTOR-activity. Similarly, this could again aid patient selection in the future for MAPK- and PI3K-AKT-mTOR pathways-based targeted therapies [188–190]. An important limitation for the gene pathway analysis was, nevertheless, the heterogeneity of the imaging features within the particular imaging feature groups. To minimize this effect, specific subgroups were created such as “enhancement patterns” and “amount of enhancement”. Another important limitation for this analysis was that different types of genomics information (e.g. gene mutation vs gene expression) were described in literature. In addition to that, alterations can in principle result in either the activation or repression of the involved gene. In the performed analysis, the direction of the change, activation versus repression, could not be taken into account. Therefore, this analysis could only reveal associations.

Although evidently standardised imaging features and genetic tests are needed for further validation, results of this gene pathway analysis do reveal that oncology-wide associations between imaging groups and oncology pathways with potentially clinical value may exist. Our
findings do not only indicate radiophenotype-genotype associations could be similar in different cancer types, but also imply that radiogenomics could aid patient selection and monitoring of pathway-targeted treatment in the future.

**Radiogenomics techniques**

Different approaches were seen for conducting radiogenomics analysis. A considerable disadvantage of qualitative imaging assessment is the poor interobserver agreement. A powerful tool to overcome this is a validated feature set, such as VASARI [191] for glioma imaging [58, 60, 64, 192]. The rapidly rising capacity of quantitatively computer-extracted imaging (perfusion-, diffusion- and texture features) enables more powerful and robust prediction of genomic traits. This radiogenomic approach has proven to be powerful for prognosis-prediction [58–64, 97, 99, 142], and for revealing differential pathway-activity [60, 148, 193, 194]. The trend in radiogenomics is increasingly headed towards models of multiparametric multilevel (clinical, radiological and histopathological) data, unravelling radiogenomic networks [58, 63, 64, 105, 116]. Methodologically, however, the use of quantitative imaging is still developing. Reproducibility of quantitative parameters is a major concern, since they are highly dependent on scanner systems and software packages. Particularly in MRI, it remains challenging, as it has less standardised quantitative values compared with CT- or PET-imaging. Moreover, overfitting of data models can be an issue. Standardised datasets such as The Cancer Imaging Archive (TCIA) [195] and The Cancer Genome Atlas (TGCA) [196] can provide a solution for validation in an independent cohort. Standardization of methods and prospective validation are needed before quantitative radiogenomics can be treatment informative.

**Limitations**

A limitation of this study was the marked heterogeneity of genomic and imaging features and the variety of analysing methods which made data integration challenging. Another constraint was that the effect size and the direction of associations were not always reported. There might have been publication bias for significant findings, but the novelty of this field of research reduces this risk. A limitation was that data of included multiparametric modelling studies were usually not published online, so these p-values could not be incorporated in the database.

**Potential of radiogenomics**

Radiogenomic genotyping has the advantage that it can capture tumor heterogeneity, can be performed repeatedly for treatment monitoring, and can be performed in malignancies for which biopsy is not available. Moreover, radiogenomics is cost-effective using routine clinical imaging for analysis. The gene pathway analysis in this study revealed imaging-genomic networks in oncology and indicated that radiogenomics may be suitable for predicting efficacy of pathway-targeted therapies. Although an extensive amount of potentially valuable radiogenomic biomarkers was identified, validation studies are needed since the robustness of features obtained by different scanners remains an important concern. This study provides an extensive database of imaging-genomic associations that can guide future research to developing radiogenomic tools for treatment selection and prognosis prediction in human oncology. Radiogenomics, connecting multiparametric quantitative imaging with genomic data, yields great potential for non-invasive genotyping, thereby contributing to the shift towards precision medicine in oncology.

**METHODS**

We performed this study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [197].

**Search strategy and article selection**

We systematically searched the Medline and Embase databases for English literature published until 1-2-2017 on radiogenomics in oncology with search terms referring to radiogenomics and oncology (Supplementary Table 1). References of included articles and literature reviews were checked for additional eligible studies. The following inclusion criteria were adopted: (1) the population consisted of human cancer patients; (2) the article comprised statistically assessed associations between imaging features on CT, MRI, FDG-PET or mammography and genomics; and (3) full-text was available in English. We excluded studies performing radiogenetics using immunohistochemistry analysis. We excluded case reports, editorial letters, and reviews.

**Extraction of study characteristics, quality checklist**

Study characteristics, quality assessment, p-values for associations and effect measures were incorporated in a database (Supplementary Table 2). P-values of studies using an extensive amount of quantitative imaging features or multiparametric models were reviewed separately. For quality assessment, the QUADAS-2 checklist [198] was used, with additional items to address radiogenomics specifically, including the availability of an independent validation cohort. All data generated or analysed during this study are included in this published article (and its Supplementary Information files).
Oncology-wide gene pathway analysis

Gene pathway analysis was performed to examine concordance between grouped radiophenotypes oncology-wide and gene pathways. For this analysis, imaging features were classified for 14 coherent imaging groups. Significant radiogenomic associations for each imaging group were selected. Only single genes were selected (e.g. no chromosome-type aberrations), and the genes were annotated according to the HUGO Gene Nomenclature Committee (HGNC) nomenclature, regardless of neoplasm location or type of genetic information (DNA mutation, gene expression (mRNA), methylation status). A minimum of 20 genes per imaging feature group was required for inclusion in the analysis. Gene pathway analysis was performed by comparing significantly associated genes within a particular imaging group with already existing functional gene pathway annotations; the cancer gene pathways in the Kyoto Encyclopaedia of Genes and Genomes (KEGG) database [193, 199]. The ToppGene Suite software (Division of Biomedical Informatics, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; https://toppgene.cchmc.org/) was used for gene pathway analysis based on functional annotation, calculating p-values using the hypergeometric probability mass function method. P-values were corrected for multiple testing using the Bonferroni method (cutoff value 0.05).

Author contributions

P.G. and M.C.J. contributed to the design and supervision of this study. M.C.J. and R.W.J. created the search strategy and performed the article inclusion. R.W.J. and P.A. performed the data extraction. P.G., R.W.J., P.A., R.M.M., I.E.K., and M.C.J. performed the quality assessment. All authors contributed to the data interpretation. P.G., R.W.J. and M.C.J. grouped imaging features. I.E.K. and R.W.J. performed the gene pathway analysis. All authors critically revised the article and approved the final version.

CONFLICTS OF INTEREST

The authors declare no conflicts of interests.

Note

Callouts for the below references are included into Supplementary Tables 4, 5 and 8 respectively.

[207, 208], [209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219], [220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231].

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