Predicting Response to Immune-Checkpoint Inhibition

Subjects: Pathology

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The therapeutic concept of unleashing a pre-existing immune response against the tumor by the application of immune-checkpoint inhibitors (ICI) has resulted in long-term survival in advanced cancer patient subgroups. Established biomarkers such as programmed death ligand 1 (PD-L1) and tumor mutational burden (TMB) help to select patients who will most likely benefit from ICI, however, biomarker negativity does not exclude responses. Investigating alterations in the antigen presenting pathway as well as radiomics have the potential to determine tumor immunogenicity and response to ICI. A plethora of steps is crucial for proper tumor neoantigen presentation and T cell recognition. Alterations in the antigen presenting pathway give rise to resistance mechanisms that in turn abolish the effect of ICI. Tumor neoantigen prediction models have been shown to identify cancer patients who benefit most from immune-checkpoint blockade, however, a high false positive rate is a drawback of these models. The predictive value of already established biomarkers is considerably heterogeneous across various malignancies and intratumoral and intrapatient heterogeneity complicate tumor tissue-based biomarker assessment. Radiomics offers the opportunity to evaluate biomarkers based on imaging studies without the necessity to perform tumor tissue biopsies. Several radiomics studies have shown to predict clinical outcome with ICI. Radiomics might also help to identify patients who are at risk for hyperprogressive disease upon initiation of anti-PD-1/anti-PD-L1 therapy and patients who are at risk for high grade immune-related adverse events.

Keywords: radiomics ; tumor neoantigen ; MHC ; PD-L1 ; immune-checkpoint ; T cell receptor repertoire ; beta 2 microglobulin ; loss of heterozygosity ; HLA

1. Alterations in the Antigen Presenting Pathway

The cancer immunity cycle highlights a cascade of steps which are necessitated to produce anti-tumor responses by the immune system [1]. However, a magnitude of escape mechanisms prevent tumor neoantigen recognition and in turn abolish the effect of immune-checkpoint inhibitors (ICI). These escape mechanisms are found at the DNA level (e.g., loss of neoantigens due to chromosomal instability), at the RNA level (e.g., decreased neoantigen expression due to promoter hypermethylation) as well as at the protein level (e.g., gene mutations affecting HLA heterozygosity) [2]. Currently available and/or already established predictive markers for ICI such as programmed death ligand 1 (PD-L1) [3][4][5][6] and tumor mutational burden (TMB) [7] only depict the tip of the iceberg of the cancer immunity cycle. Mutant tumor peptides have to be intracellularly processed into nine to eleven amino acid peptides, which must fit and be presented in the groove of one of the patients' surface major histocompatibility complex (MHC) I molecules [8]. Aspects of the MHC I processing and presentation pathway in order to predict tumor neoantigens, binding affinity of these tumor neoantigens to MHC I, as well as the T cell receptor (TCR) repertoire have come into the focus of immune-checkpoint blocking strategies. Despite a magnitude of evolving biomarkers for ICI and greatest interest in the gut microbiome [9], antibiotic treatment status [10][11] and T cell exhaustion markers [12], within this subsection we review the literature about tumor neoantigen presentation and prediction with regard to the application of ICI for cancer treatment.

A high TMB has been shown to be a positive predictive marker for clinical outcome with ICI across various tumor entities [13][14][15]. A higher tumor neoantigen burden is associated with improved clinical outcome in advanced non-small cell lung cancer (NSCLC) [15] and advanced melanoma [16] patients undergoing immune-checkpoint blockade and shows a strong correlation with TMB. However, mounting evidence suggests that especially patients with a high clonal neoantigen burden and a low intratumoral neoantigen heterogeneity benefit from ICI [17].

Among 77,803 identified tumor neoantigens, Rizvi et al. only found 28 (0.04%) in more than one melanoma patient [[15]. Comparable findings (99% unique neoantigens) were reported among gastrointestinal tumors [18]. These data corroborate that tumor neoantigens appear to be private events. Neoantigen binding to MHC I is the most selective step leading to peptide presentation. Only 3–4% of predicted tumor neoantigens turn out to be MHC I binders and in turn form neoepitopes [19][20]. Bjerregaard et al. investigated natural T cell responses to predicted tumor neoepitopes. Among 1948 predicted neopeptide-MHC I combinations from 13 publications, the vast majority showed a strong binding affinity to MHC I. However, only 53 neoepitopes (3%) were able to elicit T cell responses [21].

Tumor neoantigen prediction models (as summarized in Table 1) could be of special interest for the application of ICI and key questions to be answered by these models are: which mutated proteins are processed into eight to eleven amino acid peptides by the proteasome, and are transferred into the endoplasmatic reticulum by the transporter associated with antigen processing (TAP), and are loaded onto one out of six MHC I molecules in the individual patient (about 12,000 human leukocyte antigen (HLA) alleles identified in the human population [22]), and are shuttled to the cell surface by chaperone proteins in order to be recognized by cytotoxic T-lymphocytes [23].

Table 1. Overview of (tumor) neoantigen prediction models.

Reference	Publication Date	Author
[24]	1998	Mamitsuka et al.
[25]	2002	Dönnes et al.
[26]	2003	Nielsen et al.
[27]	2005	Larsen et al.
[28]	2006	Antes et al.
[29]	2007	Nielsen et al.
[30]	2008	Lundegaard et al.
[31]	2009	Hoof et al.
[32]	2009	Zhang et al.
[33]	2009	Kim et al.
[34]	2011	Lundegaard et al.
[35]	2013	Calis et al.
[30]	2014	Yadav et al.
[36]	2015	Pedersen et al.
[37]	2016	Andreatta et al.

[38]	2016	Nielsen et al.
[39]	2016	Kalaora et al.
[40]	2017	Jurtz et al.
[41]	2017	McGranahan et al.
[42]	2017	Luksza et al.
[43]	2018	O’Donnell et al.
[44]	2018	Kim et al.

Each of the aforementioned steps is crucial for proper tumor neoantigen presentation. Down-regulation of TAP1 (e.g., by promoter methylation) is associated with a lower infiltration of tumor infiltrating lymphocytes (TILs) and with an inferior clinical outcome in early colorectal cancer (CRC) [[45] and genetic variants of TAP are associated with the development of high-grade cervical neoplasia [46]. Lower expression of HLA class I genes as well as of beta-2 microglobulin (β2m) are immune escape mechanisms in NSCLC [17][47][48] and melanoma [49] patients undergoing immune-checkpoint blockade. HLA class I loss has been shown to prevent continuous T cell recognition in a human melanoma model [50]. HLA-A down-regulation is mediated e.g., by the RNA-binding protein MEX3B [51], by loss of function mutations in the genes encoding the interferon-receptor associated Janus kinase 1 (JAK1) or Janus kinase 2 (JAK2) [52][53][54] or by truncating mutations in the gene encoding beta 2 microglobulin (β2m) [52]. A major impact of HLA class I genotype on clinical outcome with ICI has been corroborated by Chowell et al. HLA-I homozygosity in at least one locus was associated with an inferior survival in two independent cancer cohorts undergoing immune-checkpoint blockade and proved as an independent predictor of survival in multivariate analysis. The combined effect of HLA class I genotype and TMB on survival was greater than the effect of TMB alone [55]. In a similar approach, Goodman et al. reported a better discrimination of survival among TMB high cancer patients undergoing immune checkpoint blockade by considering the MHC I genotype [56]. Prediction models such as the Loss of Heterozygosity in Human Leukocyte Antigen (LOHHLA) bioinformatics tool enable estimation of allele-specific HLA loss from sequencing data and improve neoantigen prediction accuracy [41]. Hopkins et al. examined the role of the peripheral TCR repertoire in immunotherapy treated pancreatic adenocarcinoma. A low baseline clonality as well as a high number of expanded clones following treatment with cytotoxic T-lymphocyte protein 4 (CTLA-4) targeting ipilimumab was associated with a statistically significantly longer survival. The latter results were not reproducible with programmed cell death protein 1 (PD-1) targeting therapy [57]. Comparable findings concerning TCR repertoire dynamics [58] and clinical outcome [58][59] with anti-CTLA-4 and anti-PD-1 targeting therapy were reported in advanced melanoma patients [58]. Despite the limited number of patients included in the aforementioned retrospective analyses, the opposite impact of baseline TCR clonality on clinical outcome with anti-CTLA-4 and anti-PD-1 targeting therapy is hypothesis generating and suggests sequential immunotherapy strategies of anti-CTLA-4 followed by anti-PD-1 targeting therapy.

A high false positive rate remains a major drawback of tumor neoantigen prediction algorithms. MHC class I binding affinity (calculated as the wild-type peptide binding affinity relative to the mutant peptide binding affinity) was demonstrated to be a major determinant of cancer peptide immunogenicity and outperformed TMB as well as neoantigen burden for clinical outcome in melanoma and NSCLC patients undergoing immune-checkpoint blockade [60]. In an integrative approach, Kalaora et al. combined whole-exome and RNA sequencing with MHC-peptidomics (analysis of peptide binding to MHC I by liquid chromatography and tandem mass spectrometry) and the neoantigen prediction tool NETMHCpan in advanced melanoma patients. In a direct comparison, this prediction tool, which integrates binding affinity data and mass spectrometry data, outperformed other neoantigen prediction alogorithms [39]. The latter approach highlights the advantage of combining bioinformatic neoantigen prediction with MHC-peptidomics in order to reduce the rate of false positive neoepitopes, especially in cases of rare HLA allotypes [20][61].

However, peptides with a predicted high MHC I binding affinity are not necessarily immunogenic. In neoepitope prediction strategies, attempts such as the integration of information concerning the hydrophobicity of the TCR contact region [44][62], amino acid characteristics [35] or binding differences between wild-type and mutant epitopes [40] yield at increasing the probability to identify clinically relevant neoepitopes [44]. Calis et al. reported two common properties of neopeptide-MHC combinations, which cause differences in T cell recognition: (1) the composition of amino acids in the position 4-6 of the presented peptide as well as (2) the size and absence/presence of aromatic side chains [35]. Neopepsee, a machine-learning-based neoantigen prediction program, integrates nine immunogenicity features including the aforementioned features and was able to determine immunogenic neoantigens in melanoma and chronic lymphocytic leukemia (CLL). Furthermore, the presence of immunogenic neoantigens determined by Neopepsee was associated with a better prognosis in patients with gastric cancer [40]. Luksza et al. combined estimations of the probability that a neoantigen will be presented on MHC I and the probability that presented neoantigens will be recognized by the TCR repertoire based on tumor clonality, MHC I binding affinity and microbial epitope homology. This model was applied to two melanoma cohorts and one NSCLC cohort undergoing anti-CTLA-4 and anti-PD-1 targeting therapy, respectively, and predicted survival in each cohort [37]. Snyder et al. developed a bioinformatic pipeline incorporating MHC class I binding probability, TCR binding probability, patient specific HLA genotype and epitope-homology analysis in order to identify putative neoepitopes associated with clinical outcome in advanced melanoma patients undergoing anti-CTLA-4 targeting therapy. Among predicted neoantigens, conserved stretches of amino acids were identified that were shared by patients with clinical benefit exceeding six months. These neoepitope signatures were significantly associated with survival in the discovery as well as in the validation set [63]. Published studies evaluating the antigen presenting pathway and TCR repertoire by artificial intelligence and the impact on clinical outcome in patients undergoing immune-checkpoint blockade are summarized in Table 2.

Table 2. Impact of the antigen presenting pathway and T cell receptor (TCR) repertoire on clinical outcome with immune-checkpoint inhibitors (ICI).

Reference	Author	Tumor Entity	Findings
[17]	McGranahan et al.	NSCLC, melanoma	↑ PFS/OS with high clonal neoantigen burden + low intratumoral neoantigen heterogeneity
[47]	Gettinger et al.	NSCLC	β2m loss drives resistance to ICI
[48]	Sade-Feldman et al.	melanoma	β2m LOH drives resistance to ICI
[55]	Chowell et al.	solid tumors	↑ OS with maximal heterozygosity at HLA-I loci
[56]	Goodman et al.	solid tumors	↑ ORR/PFS/OS prediction by MHC I genotype analysis among TMBhigh tumors
[57]	Hopkins et al.	pancreatic ductal adenocarcinoma	↑ OS with low baseline TCR clonality before anti-CTLA-4 Tx ↑ OS with higher number of expanded TCR clones following anti-CTLA-4 Tx

[59]	Hogan et al.	melanoma	↑ ORR/PFS with low baseline TCR clonality in anti-CTLA-4 treated patients ↑ ORR/PFS with high baseline TCR clonality in anti-PD-1 treated patients
[60]	Ghorani et al.	NSCLC, melanoma	↑ PFS/OS prediction by assessment of differential binding affinity of mutated peptides for MHC I compared to TMB or tumor neoantigen burden
[42]	Luksza et al.	NSCLC, melanoma	OS discrimination based on neoantigen MHC I binding affinity and T cell recognition
[63]	Snyder et al.	melanoma	OS prediction based on neoantigen MHC I binding probability, TCR binding probability, HLA genotype and epitope-homology analysis

PFS: progression-free survival; OS: overall survival; MHC: major histocompatibility complex; TCR: T cell receptor; HLA: human leukocyte antigen; ORR: overall response rate; NSCLC: non-small cell lung cancer; β2m: beta-2 microglobulin; ICI: immune-checkpoint inhibitor; LOH: loss of heterzygosity; TMB: tumor mutational burden; CTLA-4: cytotoxic T-lymphocyte protein 4; Tx: therapy; PD-1: programmed cell death protein 1;.

A plethora of previous studies have focused on individual factors affecting the success of immune-checkpoint blockade in immuno-oncology. However, a comprehensive analysis incorporating multiple factors is of utmost importance. Apart from the antigen presenting pathway, future models predicting clinical outcome with ICI necessitate the integration of additional factors affecting the tumor-host interaction such as PD-L1 expression, gut microbiota composition, patient germline genetics, immune microenvironment composition as well as absence/presence of soluble inhibitory molecules as proposed in several cancer immunograms [12][64][65]. For such an approach, DNA sequencing data of the tumor, RNA sequencing data of the microenvironment and germline DNA sequencing will be required. In this regard, Xie et al. developed a multifactorial deep learning model integrating microsatellite instability (MSI-H) burden, somatic copy number alteration (SCNA) burden and modified TMB (mTMB) into four genomic clusters. Data were derived from 8,646 samples of The Cancer Genome Atlas (TCGA) across 29 tumor types. Interestingly, the abovementioned genomic features only showed a weak to moderate correlation, suggesting that each feature has a distinct impact on tumor biology. The authors used TCGA RNA sequencing data to characterize the tumor microenvironment of each genomic cluster by the level of TIL infiltration, expression of immune genes and status of immune pathways. Each cluster was associated with a unique immune landscape. Genomic clusters discriminated patients with different risk for OS in the entire cohort as well as in multiple cancer types. When applying these four genomic clusters to two anti-CTLA-4 treated melanoma cohorts, cluster 4 (MSIhigh, SCNAhigh, mTMBlow) showed the lowest rate of clinical benefit and the shortest OS [66].

However, prospective validation and reproducibility in a real-world setting will be prerequisites for applying such prediction models in clinical practice.

2. Radiomics

In general, the assessment of predictive biomarkers for ICI is frequently limited by the availability of tumor tissue, intralesional as well as interlesional tumor heterogeneity [67] and by expression dynamics during the course of disease [68] and necessitates invasive procedures with relevant periprocedural risks [69][70] in often comorbid cancer patients.

Due to the availability of routinely performed imaging studies and correlations of images with underlying biological processes radiomics may serve a new predictive tool in immuno-oncology in the near future. Apart from non-invasive identification of potential responders to ICI, addressing resistance mechanisms as well as visualization of drug distribution and of the tumor microenvironment are major goals of radiomics in immuno-oncology. Radiomics is based on common

imaging modalities such as computed tomography (CT), positron emission tomography (PET) and magnetic resonance tomography (MRT) and necessitates the following steps: image acquisition, identification of the target volumes, segmentation, feature extraction and analysis [71].

2.1. Assessment of Mutation Status by Radiomics

CT-based radiomic features are associated with molecular aberrations [72][73][74][75] in various types of cancer. Yang et al. found a highly statistically significant association between a CT-based radiomic signature and KRAS/NRAS/BRAF mutations in a test cohort of 61 CRC patients (area under curve (AUC): 0.869, $p < 0.001$) and confirmed the results in a validation cohort [72]. In the light of the recently reported positive predictive value of KRAS mutations for pembrolizumab monotherapy response in the KEYNOTE-042 study [76] such a radiomic approach could be of clinical relevance for treatment decisions in advanced non-squamous NSCLC. Mismatch repair deficient (dMMR) tumors harbor high numbers of mutation-associated neoantigens and are considered sensitive to ICI [77]. The latter finding in turn has led to the tissue/site-agnostic approval of pembrolizumab in dMMR solid tumors by the FDA. Huang et al. demonstrated the feasibility to assess the mismatch repair status by a CT-based radiomic signature in a test cohort of 140 CRC patients (AUC: 0.914, $p < 0.001$) and confirmed the good discrimination in a validation cohort including 114 CRC patients (AUC: 0.702, $p = 0.012$) [73]. Due to the low frequency of dMMR solid tumors in advanced stages [77], this radiomic approach will only identify a minority of potential responders to ICI. NSCLC harboring activating EGFR mutations are insensitive to ICI monotherapy [78][79]. Yip et al. showed the potential of quantitative CT imaging to predict the EGFR mutation status in operable NSCLC patients in the perioperative setting (AUC: 0.67) [176]. Comparable findings based on FDG-PET CT imaging were described by Gevaert et al. in stage 1–4 NSCLC patients (AUC: 0.89) [75].

2.2. PD-1/PD-L1 Expression and Heterogeneity Assessed by Radiomics

CT based radiomic features are capable of separating patients with NSCLC [80][81][82][83][84] as well as head and neck squamous cell carcinoma (HNSCC) [81] with differing risk profiles for survival. Furthermore, CT based radiomic approaches allow prediction of dichotomous PD-L1 expression on tumor cells (tumor proportion score: TPS) [82][83] and density of CD3+ [82] or CD8+ [85] TILs in NSCLC. Successful anti-PD-1/anti-PD-L1 receptor-ligand-pair imaging by PET scans in mice with subcutaneously injected melanoma cells was demonstrated by Hettich et al. [86]. In a similar approach, Xing et al. [87] and Niemeijer et al. [88] investigated the correlation between PD-L1/PD-1 expression based on single photon emission computed tomography (SPECT), PD-L1/PD-1 PET and PD-L1/PD-1 expression assessed by immunohistochemistry (IHC) in NSCLC patients. Xing et al. used the anti-PD-L1 antibody NM-01, site-specifically labeled with technetium-99m, for SPECT imaging in 16 NSCLC patients (including squamous and non-squamous histology) in order to correlate tumor uptake with PD-L1 IHC. Patients with a PD-L1 expression ≤1% demonstrated statistically significantly lower tumor to peripheral blood tracer uptake ratios (mean 1.89 vs. 2.49, $p = 0.0048$) with a corresponding AUC of 0.88. It is noteworthy that four out of twelve patients with lymph nodes metastases showed considerable intra-patient differences (>20%) of PD-L1 expression [87]. Niemeijer et al. reported a statistically significant correlation between radiotracer uptake (18F-BMS-986192, standardized uptake value: SUV) and PD-L1 expression based on IHC (PD-L1 ≥50%: SUVpeak 8.2 versus PD-L1 <50%: SUVpeak 2.9, $p = 0.018$). The observed heterogeneous intrapatient and interpatient radiotracer uptake highlights the challenge to adequately assess tumor PD-L1 expression by core needle biopsies [88]. The latter two studies prove the feasibility to assess locoregional differences of PD-L1 expression in primary tumors and distant metastases. The assessment of intrapatient PD-L1 expression heterogeneity by radiomics may facilitate treatment decisions concerning intensity of therapy (ICI monotherapy versus ICI combined with chemotherapy) in clinical practice.

2.3. Radiomics Predict Clinical Outcome with ICI Therapy

By combining CT images and RNA-sequencing genomic data from tumor biopsies of patients with advanced solid tumors (MOSCATO trial) [89], Sun et al. developed a radiomic signature that could discriminate between high (>median) and low (<median) density of CD8+ TILs (AUC: 0.74,
$p < 0.0001$) [85] and validated the findings in three independent advanced solid tumor cohorts: TCGA validation set [90], tumor immune phenotype validation set [91] and immunotherapy-treated validation set [92]. Patients with a high radiomic score
(CD8+ TILs > median) showed a statistically significantly increased median OS (24.3 versus 11.5 months, $p = 0.0081$) in the immunotherapy-treated validation set and the radiomic score proved to be the strongest independent prognosticator for OS in multivariate analysis (hazard ratio (HR): 0.52,
$p = 0.0022$) [85]. Bensch et al. found a better correlation between clinical outcome and PD-L1 status assessment by PET imaging (89Zr-atezolizumab) in comparison to PD-L1 evaluation by IHC or RNA-sequencing data in 22 patients undergoing treatment with atezolizumab for bladder cancer, NSCLC or TNBC [93]. Khorrami et al. evaluated changes in

the radiomic texture during two to three cycles of ICI therapy and reported the “delta-radiomic risk-score“ to predict response as well as OS with ICI in NSCLC [94]. Trebeschi et al. developed a radiomic signature based on pre-treatment CT images on a lesional level in advanced NSCLC and melanoma patients undergoing anti-PD-1 therapy. These radiomic features were significantly associated with response in pulmonary and nodal NSCLC metastases, whereas the model performed poorly on pulmonary and hepatic melanoma metastases. However, the model statistically significantly predicted OS in both tumor types (NSCLC: AUC: 0.76, $p < 0.01$; melanoma: AUC: 0.77, $p < 0.01$) [95]. Correlations of CT-based radiomic features and therapy response were also reported for patients with advanced ovarian cancer [96] and bladder cancer [97] undergoing immune-checkpoint blockade. Table 3 summarizes radiomics studies predicting clinical outcome with immune-checkpoint blockade.

Table 3. Prediction of clinical outcome by radiomics in cancer patients undergoing immune-checkpoint blockade.

Reference	Author	Tumor Entity	Findings
[85]	Sun et al.	solid tumors	OS prediction based on radiomics CD8+ cell score
[93]	Bensch et al.	bladder cancer, NSCLC, TNBC	↑ ORR/PFS/OS prediction by PET evaluation with zirconium-89-labeled atezolizumab compared to IHC or RNA-sequencing based PD-L1 assessment
[94]	Khorrami et al.	NSCLC	ORR and OS prediction based on changes in radiomic texture (“DelRADx”)
[95]	Trebeschi et al.	melanoma, NSCLC	Response prediction of individual metastases and OS prediction based on multiple radiomic features
[96]	Himoto et al.	ovarian cancer	Prediction of clinical benefit by intratumoral heterogeneity (radiomic feature) and by number of disease sites
[97]	Ligero et al.	solid tumors	↑ ORR prediction by clinical-radiomics signature score
[98]	Tunali et al.	NSCLC	Prediction of hyperprogressive disease based on clinical-radiomic models
[99]	Dercle et al.	non-squamous NSCLC	PFS prediction based on tumor volume reduction, infiltration of tumor boundaries or spatial heterogeneity
[100]	Korpics et al.	solid tumors	Prediction of local tumor failure, PFS and OS in cancer patients receiving SBRT and anti-PD-1 Tx based on a radiomics score

PET: positron emission tomography; PFS: progression-free survival; SBRT: stereotactic body radiotherapy, Tx: therapy; NSCLC: non-small cell lung cancer; TNBC: triple negative breast cancer; OS: overall survival; ORR: overall response rate; IHC: immunohistochemistry; PD-L1: programmed cell death-ligand 1;

On the one hand, a subset of advanced cancer patients derives long-term survival from immune-checkpoint blockade, on the other hand, up to nine per cent of patients experience hyperprogressive disease with rapid fatal outcome upon initiation of anti-PD-1/anti-PD-L1 therapy [101]. In a clinical-radiomic approach Tunali et al. were able to identify patients with a time to progression < 2 months or hyperprogressive disease within an advanced NSCLC cohort treated with single agent or double agent immunotherapy [[99]. The latter finding is of utmost importance in clinical practice as such cancer patients should not be treated with ICI monotherapy or with ICI at all. Apart from predicting clinical outcome with immunotherapy, radiomics also has the potential to predict immune-related adverse event. In a small series of 32 advanced cancer patients, Colen et al. found radiomic features that identified the two patients who experienced immunotherapy-induced pneumonitis (accuracy: 100%, $p = 0.0033$) [102].

The abovementioned findings corroborate the potential of radiomics to visualize drug distribution, tumor characteristics as well as tumor heterogeneity and the feasibility to predict clinical outcome with ICI. However, a major caveat remains the standardization of imaging acquisition, validation in prospective clinical trials and reproducibility in a real-world setting. ICI trials in advanced solid tumors such as the “INSPIRE“ trial (NCT02644369) are prospectively investigating changes in radiomic imaging parameters as well as correlations between tumor genomic profiles and radiomic imaging signatures.

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