Imaging-based characterization of tumoral heterogeneity for personalized cancer treatment

Charakterisierung der Tumorheterogenität mittels bildgebender Verfahren zur personalisierten Krebsbehandlung

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ABSTRACT

With personalized tumor therapy, understanding and addressing the heterogeneity of malignant tumors is becoming increasingly important. Heterogeneity can be found within one lesion (intralesional) and between several tumor lesions emerging from one primary tumor (interlesional). The heterogeneous tumor cells may show a different response to treatment due to their biology, which in turn influences the outcome of the affected patients and the choice of therapeutic agents. Therefore, both intra- and interlesional heterogeneity should be addressed at the diagnostic stage. While genetic and biological heterogeneity are important parameters in molecular tumor characterization and in histopathology, they are not yet addressed routinely in medical imaging. This article summarizes the recently established markers for tumor heterogeneity in imaging as well as heterogeneous/mixed response to therapy. Furthermore, a look at emerging markers is given. The ultimate goal of this overview is to provide comprehensive understanding of tumor heterogeneity and its implications for radiology and for communication with interdisciplinary teams in oncology.

Key points:

- Tumor heterogeneity can be described within one lesion (intralesional) or between several lesions (interlesional).
- The heterogeneous biology of tumor cells can lead to a mixed therapeutic response and should be addressed in diagnostics and the therapeutic regime.
- Quantitative image diagnostics can be enhanced using AI, improved histopathological methods, and liquid profiling in the future.

ZUSAMMENFASSUNG

Im Rahmen der personalisierten Tumortherapie wird es immer bedeutender, die Heterogenität von bösartigen Tumoren zu verstehen und zu berücksichtigen. Diese kann innerhalb einer Läsion (intralesional) und zwischen mehreren Tumorläsionen auftreten, die aus einem primären Tumor hervorgehen (interlesional). Die heterogenen Tumorzellen können aufgrund ihrer Biologie unterschiedliche Reaktionen auf verschiedene Behandlungen zeigen, was wiederum das Outcome der betroffenen Patienten und die Wahl der Therapie beeinflusst. Daher sollten sowohl intra- als auch interlesionale Heterogenität in der Diagnostik berücksichtigt werden. Während genetische und biologische Heterogenität wichtige Parameter in der molekularen Tumorcharakterisierung und in der Histopathologie sind, werden sie in der medizinischen Bildgebung noch nicht routinemäßig berücksichtigt. Dieser Artikel fasst die etablierten Marker für Tumorheterogenität in der Bildgebung sowie für heterogenes/gemischtes Therapieansprechen zusammen. Darüber hinaus wird ein Ausblick über aufkommende Marker gegeben. Ziel dieser Übersichtsarbeit ist es, ein umfassendes Verständnis der Heterogenität von Tumoren und ihrer Auswir-

kungen auf die Radiologie und die interdisziplinäre Kommunikation in der Onkologie zu vermitteln.

Kernaussagen:

- Tumorheterogenität kann innerhalb einer Läsion (intralesional) oder zwischen mehreren Läsionen (interlesional) beschrieben werden.
- Die heterogene Biologie von Tumorzellen kann zu einer gemischten therapeutischen Reaktion führen und sollte sowohl bei Diagnose als auch Therapie berücksichtigt werden.
- Die quantitative Bilddiagnostik kann in Zukunft durch den Einsatz von KI, verbesserten histopathologischen Methoden und Liquid Profiling ergänzt werden.

Zitierweise

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ABBREVIATIONS

ADC	Apparent diffusion coefficient
CT	Computed tomography
ctDNA	Circulating tumor deoxyribonucleic acid
DWI	Diffusion-weighted imaging
FABPI	Fibroblast activation protein inhibitors
FDG	Fluoro-2-deoxy-d-glucose
HCC	Hepatocellular carcinoma
LP	Liquid profiling
MRI	Magnetic resonance imaging
RECIST	Response Evaluation Criteria In Solid Tumors
PET/CT	Positron emission tomography computed tomography
PSMA	Prostate-specific membrane antigen
SUV	Standard uptake value

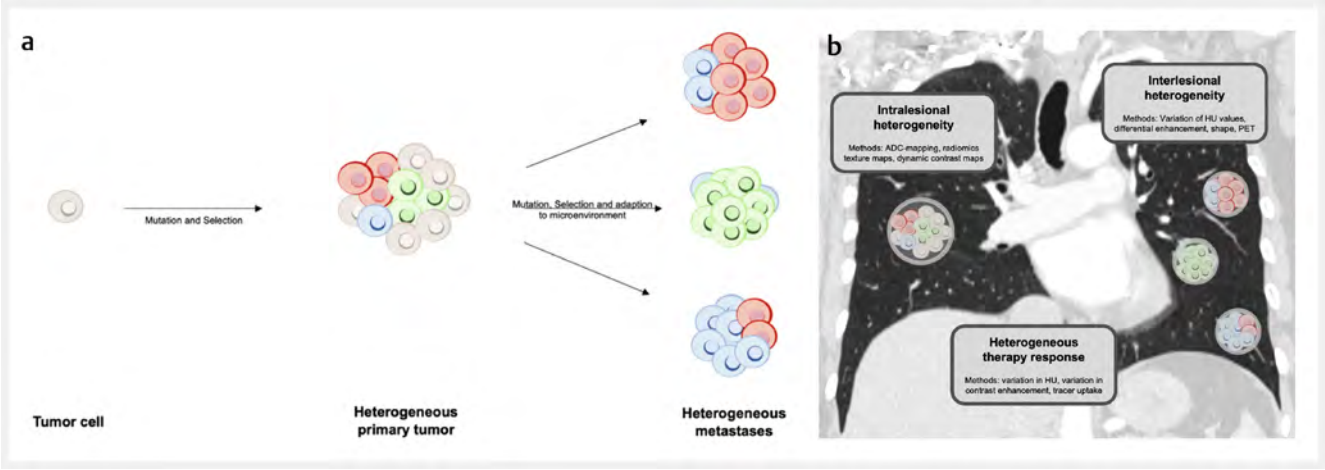
Background

Although there have been significant advancements in cancer treatment in the last few years, there is still a need for improvement. This is especially true in the context of personalized cancer treatment, which takes the variability of tumoral biology among patients with the same tumor entities into account and addresses it with corresponding targeted treatment approaches. The underlying reason for different responses to (conventional) treatments is the heterogeneity of their neoplastic biology [1]. Additionally, tumor biology not only differs between patients but there is also heterogeneity within a singular lesion (intralesional variability) and between different lesions in one patient (interlesional variability) [2, 3]. These heterogeneities manifest as morphological variations between tumor cells, genetic profiles, and the expression levels of biomarkers [4]. The variability of the tumor cells is caused by genetic heterogeneity (e. g., due to the accumulation of somatic mutations/clonal evolution) as well as non-genetic causes such as changes in the tumor microenvironment [5] (▶ **Fig. 1a**). Since tumor heterogeneity drives the emergence of resistance, it can have a major impact on patient response to therapy and thus survival [6]. Furthermore, it has been shown that increased heterogeneity of tumor lesions is linked to a worsening of patient survival [7]. Therefore, it is of crucial importance to detect both the interlesional and the intralesional tumor heterogeneity and to adapt the targeted (possibly personalized) cancer therapy to it. Despite histopathological or blood-based approaches such as Liquid Profiling (LP), modern imaging modalities and quantitative image analysis are promising devices for detecting tumor heterogeneity [8]. Since heterogeneity in or between tumoral lesions is not yet sufficiently considered in the current clinical routine, there is a need for integration of these methods, which can recognize and take heterogeneity factors into account. This review aims to give an overview of potential imaging markers for intralesional, interlesional, and response-associated tumor heterogeneity (▶ **Fig. 1b**).

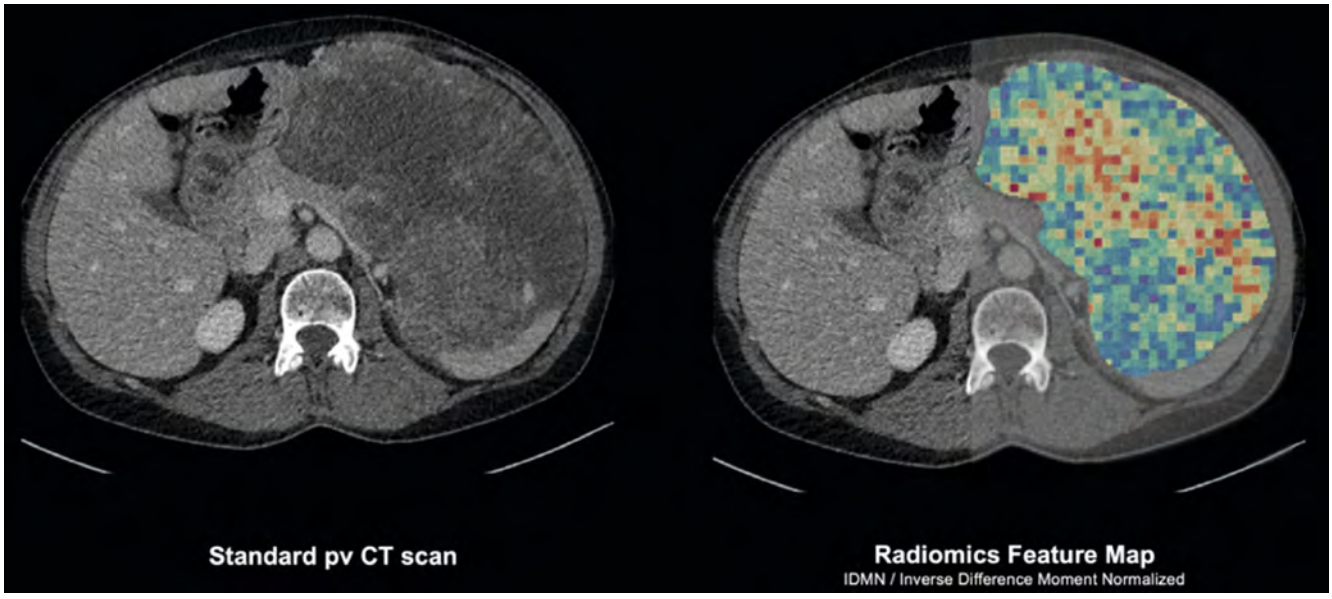
Imaging markers for intralesional heterogeneity

Traditionally, certain descriptors for specific tumoral lesions have been introduced to achieve better characterization of lesions in imaging. For example, the classification of lesion size and solid and subsolid characteristics according to the Fleischner guidelines is routinely used in the classification of incidental lung nodules [9]. Also, visual contrast enhancement, lesion size, and magnetic resonance signal (MR signal) characteristics have, as a result, been implemented in a wide variety of structured reporting schemes in oncologic imaging [10, 11]. While the multiparametric assessment of (singular) lesions has become firmly established in the clinical routine, the tumoral heterogeneity within a specific lesion is not assessed routinely in imaging.

In this context, intralesional heterogeneity is defined as the diversity of the cellular composition of a tumoral lesion, which may be assessed by imaging. For this approach, the estimation of diffusion and apparent diffusion coefficient (ADC) parametric maps on magnetic resonance imaging (MRI) are especially promising, as they allow an estimation of diffusion rates within a lesion [12]. These may vary based on the cellularity and biological properties of the local tumor environment [13, 14]. In soft tissue sarcoma, a correlation of lower ADC values with G2/3 tumor grade based on multiple intraoperative biopsies has been described [15]. For Prostate Cancer Gleason Score estimation from multiparametric MRI, an extraction of the radiomics features energy and entropy from ADC and T2 could achieve a noninvasive estimation of the underlying histology with an accuracy of up to 93 % [16]. In patients

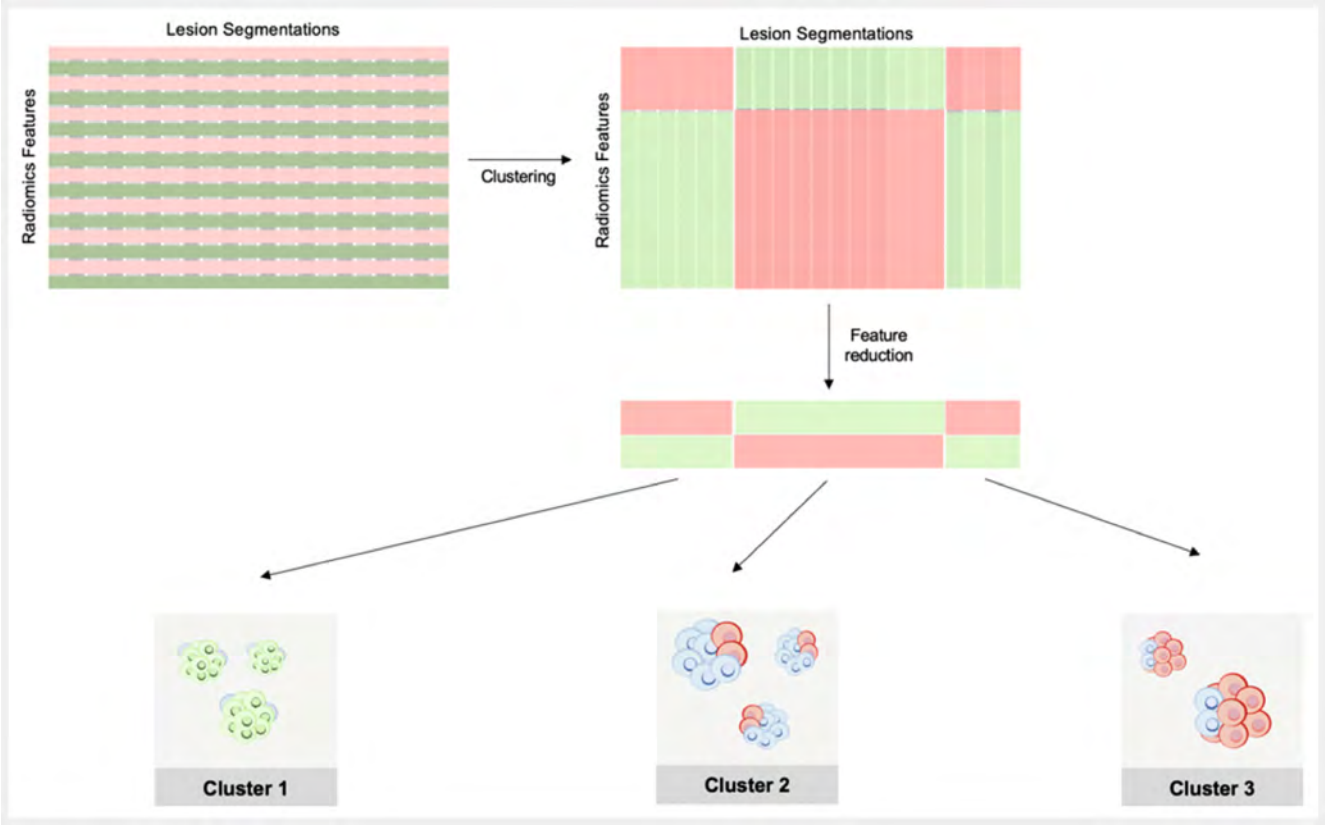


▶ **Fig. 1** **a** Mechanisms of emerging tumoral heterogeneity: Different cell types and mutation and selection of the tumor cells lead to intralesional heterogeneity. **b** Dimensions of tumoral heterogeneity. This can be identified by altering density on MRI, CT, etc. The variety between different lesions in patients with metastatic tumors can be described as interlesional tumor heterogeneity, which also can be visualized on MRI and CT, e. g. with altering diffusion, different growth patterns, or altering attenuation. Both intra- and interlesional heterogeneity can lead to a heterogeneous therapy response, which could be identified in conventional imaging or new upcoming approaches as Liquid Profiling (LP).

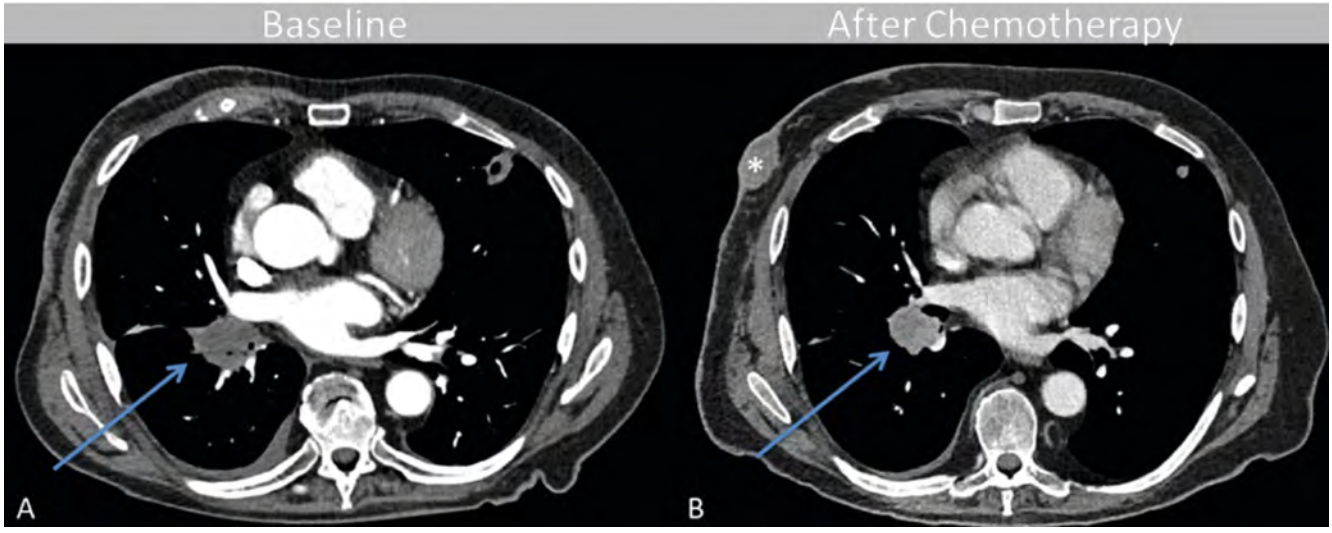


▶ **Fig. 2** Visualization of intralesional heterogeneity using a radiomics parameter map.

with lower rectal cancer, the intralesional tumor heterogeneity and therapeutic response can be predicted by diffusion-weighted MRI (DWI) [17]. Also, diagnostic MRI can be used to score heterogeneity in soft tissue sarcoma und identify them as high- or low-grade soft tissue sarcomas [18]. A direct co-registration of DWI and histology in non-small cell lung cancer showed that an estimation of the local spatial tumor cell density can be performed based on DWI data [19]. The feasibility of these methods has also been shown for perfusion MRI approaches, such as Ktrans parameter maps [20]. In a murine model, the association of multiparametric MRI data with histology and tissue biology could be shown for the estimation of malignant potential in breast cancer [21]. The intralesional differentiation of tumor tissue populations with MRI was identified in a xenograft mouse model of colorectal cancer, which allows for the differentiation of necrotic subpopulations, adipose tissue, and viable tumor. Here, ADC imaging was identified as the dominant parameter for differentiation [22]. For hepatocellular carcinoma, quantitative parameter extraction from multiparametric MRI including histogram analysis could estimate a high degree of heterogeneity within hepatocellular carcinoma (HCC) lesions [23]. Furthermore, quantitative feature extraction and visualization may help reveal novel intralesional patterns. In this context, radiomics is a good example of the unrevealed possibilities in conventional imaging such as MRI or CT. It describes



▶ **Fig. 3** Interlesional heterogeneity. Feature extraction and unsupervised clustering approach for identification of lesion clusters on imaging.



▶ **Fig. 4** Example of heterogeneous response. Axial CT scans of a patient suffering cutaneous squamous cell carcinoma. A) Baseline exam with manifestation of a pulmonary metastasis at the right hilus (arrow). B) Follow-up after chemotherapy with mixed response. The pulmonary metastasis regressed, but there is a new cutaneous metastasis at the right thoracic apparatus (*).

the abstraction of parameters from diagnostic images, which are not recognizable to the human eye [24, 25]. The potential of radiomics for the detection of tumor heterogeneity has been demonstrated several times for different tumor entities such as breast cancer [26–28] or hepatocellular carcinoma [29–31].

▶ **Fig. 2** shows the example of a patient with sarcoma. In the shown case, radiomics feature mapping indicates intralesional heterogeneity and may potentially help to differentiate between subregions within a lesion.

▶ **Table 1** Advanced imaging methods for the assessment of tumoral heterogeneity

Methodology	Modality	Quantified variable	Relevance for heterogeneity assessment
Spectral imaging	Dual-energy CT/photon counting CT	Energy-dependent attenuation	Enhanced iodine contrast in low-keV reconstructions and iodine mapping
Functional imaging	DWI-MRI, perfusion (MRI, CT, CEUS)	Diffusion of water molecules, perfusion	Assessment of tissue structure and cellular density
Metabolic & molecular imaging	PET/SPECT, MR-spectroscopy	Radiotracer accumulation, spectroscopy	Metabolic characterization of lesions

▶ **Table 2** Quantitative image analysis methodology for the assessment of tumoral heterogeneity.

Method	Functionality	Relevance for tumoral heterogeneity assessment
Deep learning	Use of artificial neural networks for the identification of patterns and features in medical images. Training and validation performed on large datasets	Deep learning can identify and quantify subtle patterns of tumoral heterogeneity that might be difficult for humans to detect, allowing for more precise and personalized diagnostic assessment
Geometric lesioned patterns	Location of lesions (e. g., within organ) and their positions respective to each other	Characterization of metastatic and lesional patterns as well as their development over time
Radiomics	Extraction of predefined, quantitative features from region of interest describing shape, texture, intensity.	Visualization of tumoral heterogeneity, prediction of response, preparation of imaging data for big data analysis
Traditional signal/ attenuation measurements	Measurement of mean/SD of signal or CT attenuation in Hounsfield units	Indirect measurement of contrast agent attenuation, quantification of restricted diffusion. and simple estimation of lesion characteristics
Volumetry	Traditional measurements of lesions such as shape, size, volume. Can be performed manually, semi-automatically or automatically	Assessment and quantification of heterogeneous tumoral response. Starting point for further quantitative analyses

Besides the mentioned imaging modalities and markers, molecular imaging modalities are also promising in the noninvasive characterization of tumor heterogeneity.

One example is the combination of positron emission tomography and computed tomography (PET/CT) using tracers such as radioactively labelled 2-[(18)F]fluoro-2-deoxy-d-glucose (FDG), which is taken up by tumor cells. The uptake of the radioactively labeled substance provides information about the cell's metabolism [32]. Using 18-F FDG PET/CT metabolic tumor volume and intralesional tumor heterogeneity of pancreatic adenocarcinomas, rectal cancer and many other malignancies can be detected [33–36]. Furthermore, in metastatic breast cancer and colorectal cancer, intralesional tumor heterogeneity determined by 18F-FDG PET/CT can be used as a predictor of therapy response [37–39].

Imaging markers for interlesional heterogeneity

Compared to localized oncologic disease, metastatic disease poses an even more complex challenge in terms of tumoral heterogeneity, because not only biological heterogeneity within the primary lesion but also between metastatic lesions becomes relevant. While this interlesional heterogeneity can be clearly understood as a biological reason for mixed response to treatment, it has not yet been addressed comprehensively in clinical imaging. A study by Siravegna et al. addressed the clonal evolution of cancer foci in metastatic colorectal cancer and investigated the per-lesion heterogeneity in a post-mortem biopsy approach [40]. It shows the importance of a per-lesion investigation of aggressiveness, since per-lesion genetic patterns and evolutionary dynamics were associated with per-lesion response to systemic therapy. In particular, this study showed an association between resistance patterns and lesion response according to Response Evaluation Criteria in Solid Tumors (RECIST).

Despite genetic approaches, the heterogeneity of lesions in imaging is mainly evaluated qualitatively or in terms of response assessments. Partly, associations between mutational patterns in lesions have been described, for example, an association of lower ADC values on MRI [41] and higher standard maximal uptake values (SUVmax) on PET/CT [42] with KRAS mutations in colorectal liver metastases. While a visual classification of lesions in metastatic disease may be partly performed in terms of enhancement or size, the discretization and quantification of lesion texture utilizing the radiomics workflow and/or convolutional neural networks may allow for a more precise classification of lesions (workflow shown in ▶ **Fig. 3**): In the case of metastatic colorectal cancer, radiomics feature extraction and unsupervised hierarchical clustering have been employed to define lesion subtypes (small disseminated, heteroge-

▶ **Table 3** Overview of evidence regarding the assessment of tumoral heterogeneity in imaging.

Year	Author	Journal	Modality	Tumor entity	Methods	Findings	Approach	PMID
Intralesional heterogeneity on CT imaging								
2014	Aerts H et al.	Nature communications	CT	Lung, head/neck	Radiomics extraction, clustering	Prognostic phenotype	Intralesional	24892406
2013	Ganesham B et al.	BMC cancer imaging	CT	Various	Histogram analysis	Estimation of heterogeneity	Intralesional	23545171
2021	Yousefi B et al.	Nature Sci Rep	CT	NSCLC	Radiomics extraction, clustering	Association of radiomics phenotypes with response	Intralesional	33976268
2020	Steinacker JP et al.	Visc Med	CT	Pancreatic	Radiomics extraction	Kurtosis negatively associated with progression	Intralesional	33718486
2022	Enke JS et al.	Cancers	CT	Lymphoma	Radiomics	Radiomics can differentiate subtype differentiation	Intralesional	35158980
Intralesional heterogeneity on PET and MRI imaging								
2012	Hilario A et al.	AJNR	MRI	Gliomas	ADC, CBV	Minimum ADC combined with maximum rCBV improves glioma grading on MRI	Intralesional	22207304
2015	Fehr D et al.	Proc Natl Acad Sci USA	MRI	Prostate	Radiomics	Radiomics classification correlates with Gleason grade	Intralesional	26578786
2017	Bowen SR	J Magn Reson Imaging	MRI, PET	Cervical cancer	Histogram analysis	Features are associated with response to radiotherapy	Intralesional	29044908
2017	Hectors SJ et al.	nature Sci Rep	MRI	HCC	Histogram analysis	Histogram data correlated with histopathology	Intralesional	28550313
2018	Yin Y et al.	IEEE Trans Med Imaging	MRI	Lung	Quantitative DWI	Association of DWI with tumor cell load and heterogeneity	Intralesional	28463188
2019	Mao W et al.	Abdom Radiol	PET	Colorectal	SUVmax quantification	SUVmax associated with KRAS mutations	Intralesional	30143816
2020	Gültekin MA et al.	Eur J Radiol	MRI	Colorectal	ADC quantification	ADC associated with presence of KRAS mutation	Intralesional	32109834
2021	Girot C et al.	MAGMA	MRI	Colorectal (murine model)	Ktrans perfusion maps, clustering	Ktrans maps can be classified by clustering	Intralesional	34091826
2021	Lau D et al.	J Immunother Cancer	MRI	Melanoma	DWI and perfusion parameters	Ktrans and DWI quantification associated with successful response to immunotherapy after 12 weeks	Intralesional	34561275
2022	Gerwing M et al.	Front Oncol	MRI	Breast (murine model)	Multiparametric MRI	Heterogeneity of multiparametric MRI was associated with aggressive potential	Intralesional	36408159
2022	Hettler M et al.	Cancers	MRI	Sarcoma	ADC quantification	ADC correlates with FNCLCC grading	Intralesional	36077866

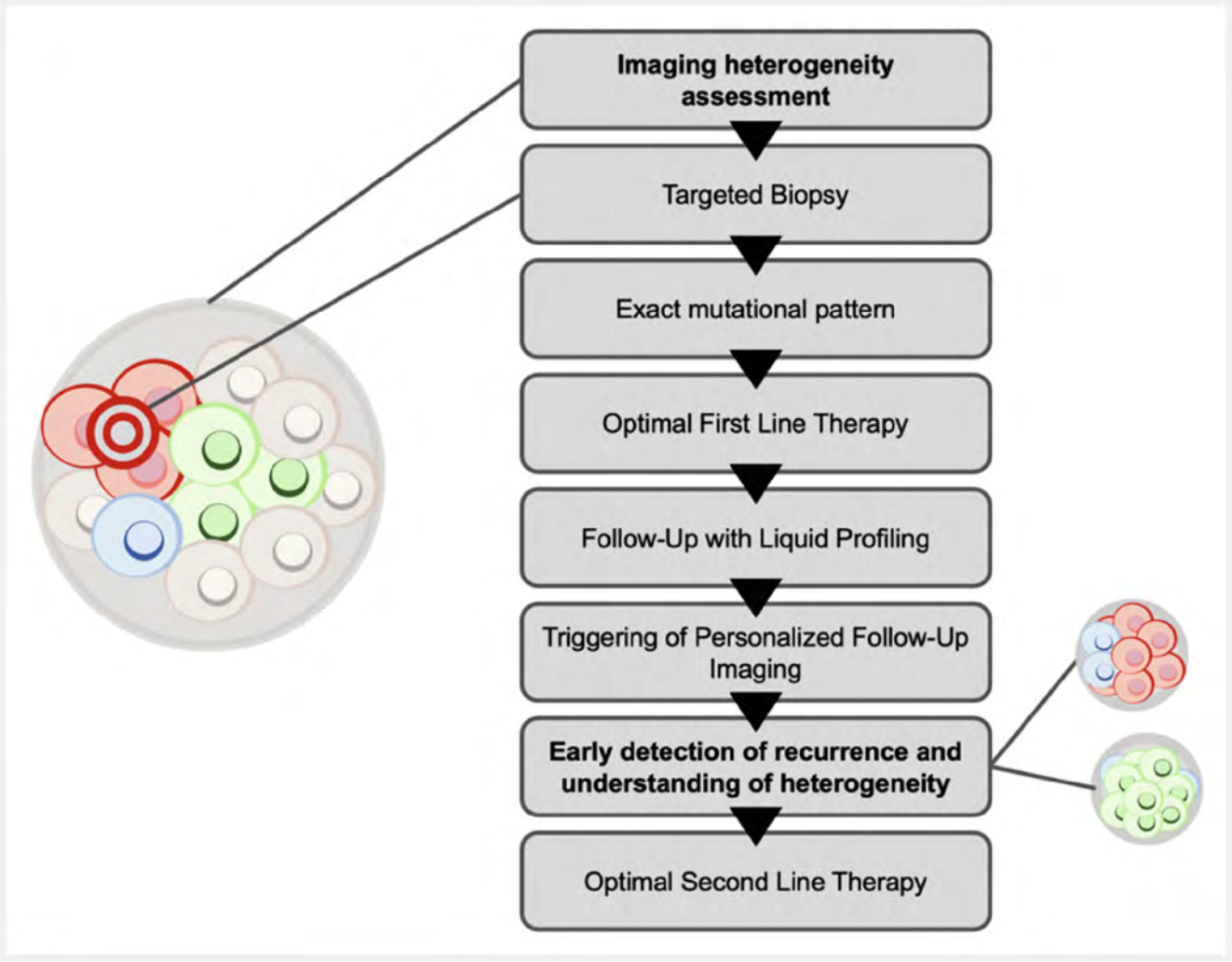
▲ **Table 3** (Continuation)

Year	Author	Journal	Modality	Tumor entity	Methods	Findings	Approach	PMID
Interlesional heterogeneity on CT imaging								
2018	Froelich MF et al.	Eur Radiol	CT	Colorectal	Mean HU extraction	Mean HU is associated with prognosis	Interlesional	29 882 070
2020	Froelich MF et al.	Clin Colorectal Cancer	CT	Colorectal	Longitudinal volumetric data	Differential response patterns of metastatic types	Interlesional	32 917 529
2022	Tharmaseelan et al.	Cancers	CT	Colorectal	Radiomics and clustering	Radiomics can be utilized to establish imaging-based lesion phenotypes	Interlesional	35 406 418
2021	Mühlberg A et al.	Eur Radiol	CT	Colorectal	Radiomics, geometric features	Features predict survival	Interlesional	32 851 450

neous, homogeneous, mixed, very large) [43]. A study by Yousefi et al. utilized cluster analysis to define two radiomics subtypes in non-small cell lung cancer lesions [44] which showed a significant association with EGFR mutation status ($p = 0.07$), progression-free survival ($p = 0.03$), and a tendency for overall survival ($p = 0.11$). Furthermore, the addition of radiomics parameters to circulating tumor deoxyribonucleic acid (ctDNA) and clinical variables resulted in a better model fit (c statistic 0.77 vs. 0.73, $p = 0.01$) for PFS. In metastatic prostate cancer, the expression of prostate-specific membrane antigen (PSMA) can vary between the different metastases as an expression of intralesional tumor heterogeneity and due to different gene expressions in the tumor cells. PSMA expression in different lesions can be detected by PET-CT [45]. Heterogeneous expression of PSMA in several lesions has the potential for a severe prognosis [46]. Another example for interlesional heterogeneity in molecular imaging is the so-called flip-flop phenomenon, which can occur in patients suffering from thyroid cancer with multiple lesions. It describes an inverse relation between iodine and glucose utilization (and uptake) in different thyroid cancer lesions according to the degree of differentiation and can lead to a mixed therapy response [47–49]. Given these facts, tumor heterogeneity is a parameter with a high prognostic value and should be monitored in the patient's follow-up.

Therapy response assessment

Intra- and interlesional tumor heterogeneity are important determiners of response to therapeutic strategies and patient outcomes [50]. The changing genetic and biological tumor signature is an evolutionary process and is often accelerated by the treatment that is used (example in ▶ **Fig. 4**) [51]. Therefore, on the one hand, the therapy strategy must be adapted accordingly. An example of this approach is the minimally invasive ablation of therapy-resistant liver lesions in patients with multiple cancer lesions, such as in oligometastatic disease with mixed response [52]. On the other hand, it is important to classify the therapy response adequately and supplement existing classifications with the parameters of lesional heterogeneity. An example of an adapted classification for HCC is presented by Zang et al. [53]. The mentioned study suggests determining the expression levels of CD45 and Foxp3 on HCC cells using immunohistochemistry in these patients. Despite molecular parameters, there is also a need to establish noninvasive image parameters. A powerful imaging parameter represents the 3 D volumetry of pulmonary metastasis in computed tomography (CT) [54]. Another prognostic marker is CT attenuation of lesions. The mean attenuation of liver lesions was identified as a predictor for therapy response of liver metastasis in colorectal cancer treated with anti-EGFR therapy [55]. Also, CT-based tumor heterogeneity analysis has the potential to predict therapeutic response in patients with pancreatic carcinoma in palliative chemotherapy [56]. A heterogeneous response can also be addressed by MRI. In this context, Lau et al. demonstrated in patients with metastatic melanoma under immune checkpoint therapy that heterogeneity of metastasis and potential therapeutic response can be visualized and assessed by MRI [57]. These data clearly demonstrate that established meth-



▶ **Fig. 5** Outlook. Emerging diagnostic approaches like integrative diagnostics and liquid profiling (LP) have major potential to improve the diagnostics and follow-up of cancer patients. Novel markers can be measured in the patient's circulation and observed during follow-up to detect recurrence early. Also, novel image markers (radiomics) will be a useful addition to standard follow-up in the future.

ods and imaging devices have the potential to visualize inter- and intratumor heterogeneity and thus a differing response to therapy. In addition to emerging approaches like liquid profiling and integrative diagnostics, it is also crucial to extract the non-human- but machine-readable information of established imaging procedures using quantitative imaging biomarkers.

Outlook

In summary, advanced imaging methods (summary given in ▶ **Table 1**) as well as quantitative data analysis approaches (▶ **Table 2**) can be utilized to evaluate tumoral heterogeneity in noninvasive imaging. An overview of the current literature is presented in ▶ **Table 3**.

Although tumoral heterogeneity and heterogeneous response should be evaluated in imaging utilizing these techniques, the optimal predictive value cannot be achieved by imaging alone. A combined approach with other diagnostic modalities such as histology, liquid profiling and molecular pathology enables a comprehensive assessment of cancer biology and the clinical situation. On the one hand, the integration of liquid profiling (LP) information with a corresponding imaging strategy can lead to earlier detection of recurrence, identify the emergence of drug resistance, and quantify minimal residual disease [58, 59]. The potential of LP to detect heterogeneity and therapy resistance was already shown in gastrointestinal cancers [60]. There is evidence that a combination of liquid biomarkers with functional imaging is helpful in the prediction of the outcome of patients suffering from castration-resistant metastatic prostate cancer [61]. Finally, LP has major potential, and it may be a powerful addition to established procedures in routine diagnostics and follow-up examinations in oncologic patients. On the other hand, imaging can guide selection of targets for biopsy to allow for a precise and optimized assessment by histopathology and molecular pathology. Therefore, better assessment of tumoral heterogeneity in diagnostic medicine will support the development of an integrative diagnostic workflow, which has important positive implications along the

whole oncology value chain [62]. Integrative diagnostics refers to the combination and joint interpretation of diagnostic results in the combination of mutual triggering of examinations and more accurate estimation of disease states, resulting in a better, personalized diagnostic strategy and more precise and actionable diagnostic results (▶ **Fig. 5**) for treatment planning [63].

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Note

This article was changed according to the Correction on December 28, 2023.

Correction

In the above-mentioned article the name of one of the authors was stated incorrectly. Correct: Christoph Brochhausen. This was corrected in the online version on December 28, 2023.