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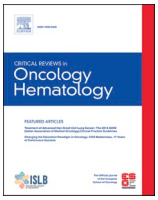

Clinical applications of radiomics and deep learning in breast and lung cancer: A narrative literature review on current evidence and future perspectives

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ABSTRACT

Radiomics, analysing quantitative features from medical imaging, has rapidly become an emerging field in translational oncology. Radiomics has been investigated in several neoplastic malignancies as it might allow for a non-invasive tumour characterization and for the identification of predictive and prognostic biomarkers. Over the last few years, evidence has been accumulating regarding potential clinical applications of machine learning in many crucial moments of cancer patients' history. However, the incorporation of radiomics in clinical decision-making process is still limited by low data reproducibility and study variability. Moreover, the need for prospective validations and standardizations is emerging. In this narrative review, we summarize current evidence regarding radiomic applications in high-incidence cancers (breast and lung) for screening, diagnosis, staging, treatment choice, response, and clinical outcome evaluation. We also discuss pro and cons of the radiomic approach, suggesting possible solutions to critical issues which might invalidate radiomics studies and propose future perspectives.

1. Introduction

In the era of personalized precision medicine, data derived from diagnostic medical images have shown a potential for clinical applications in improving decision-making process and outcome prediction when combined with clinical, pathological, laboratory and treatment characteristics (Aerts, 2016). This approach to medical imaging has created an emerging translational field of research called 'Radiomics', which is based on the hypothesis that "images are more than pictures: they are data" (Gillies et al., 2016). Radiomics is a relatively new discipline whose aim is to digitally encrypt medical images in order to extract features associated with tumour pathophysiology and microenvironment, to be finally transformed into mineable high-dimensional data (Lambin et al., 2017a). Indeed, by using computerized algorithms, quantitative features can be obtained from multimodality images, such as those derived from computed tomography (CT) scans, magnetic resonance imaging (MRI), positron emission tomography (PET)-CT scans and ultrasonography (US) (Aerts et al., 2014). These radiomic features are image-based descriptors able to quantitatively capture shape, size or volume, and texture of tumour or normal tissue regions. Once extracted, these quantitative metrics can be analysed and combined using artificial intelligence (AI) to generate predictive and prognostic models (Castiglioni et al., 2019).

The radiomics workflow consists of several essential steps, including image acquisition and pre-processing, tumour segmentation, feature extraction, knowledge discovery, and modelling (Liu et al., 2019a).

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Fig. 1 reports a graphic representation of the radiomics workflow.

Specifically, medical images are obtained using routine clinical protocols, then each tumour region of interest (ROI) is defined for analysis (i.e., tumour segmentation) including primitive lesions, regional lymph nodes and distant metastases. Different methods exist for ROI segmentation: manual delineation, which is time-consuming and is limited by inter- and intra-individual variability; and (semi-)automatic segmentation, which is recommended for reproducibility reasons, but requires a strong signal contrast between the lesion and contiguous tissues (van Timmeren et al., 2020). Thereafter, from the defined ROI, a vast amount of advanced quantitative variables is extracted via specific software programs: descriptive features can be categorised into morphological, intensity-based, texture (matrix)-based and filter-based radiomics features (van Timmeren et al., 2020). The Image Biomarker Standardisation Initiative (IBSI) was recently developed to provide a list of radiometric features with demonstrated reproducibility (Zwanenburg et al., 2020). Then, data need to be reduced through a practical selection choosing the most informative ones and combining them with additional information, such as clinic-pathological characteristics. Finally, model development and performance testing are among the most critical and demanding steps of a radiomics study (Lee et al., 2020).

Radiomics applications present several challenges: first, extracting phenotypic characteristics from routine images, and second, determining which features correlate with the underlying genotype and clinical behaviour of the disease, thus aiding in the prognostic estimation of a disease and treatment response monitoring (Hassani et al., 2019). Information derived through quantitative image analyses are used to select the most statistically significant signatures related to an outcome measure of interest and can therefore be used to develop diagnostic, prognostic and predictive biomarkers (O'Connor et al., 2017).

In recent years, deep learning (DL) has emerged alongside traditional radiomics to achieve the same goals of improving diagnostic, prognostic, and predictive modelling. Unlike radiomics, which relies on manually defined features, DL leverages convolutional neural networks to automatically learn and extract features directly from raw image data. This approach reduces the need for manual feature engineering and improves the accuracy of predictive models (Avanzo et al., 2020; Zhang et al., 2022a).

Radiomics and DL have shown great potential and, in the last few years, an increasing amount of evidence has been accumulating regarding its potential clinical applications in many crucial moments of cancer patients' history, including screening, diagnosis, staging, treatment choice, response, and clinical outcomes evaluation (see Fig. 2).

The aim of the present work is therefore to provide a complete overview of the potential clinical applications of radiomics and DL in the field of oncology, by reviewing and discussing current evidence in lung cancer (LC) and breast cancer (BC) (Wu et al., 2021; Anan et al., 2022).

2. Radiomics application in oncology

LC represents the leading cause of cancer-related deaths worldwide due to its high incidence and its frequent onset at advanced-stage (Siegel et al., 2018). Despite significant diagnostic and therapeutic improvements, there is still a lack of predictive and prognostic biomarkers, which translates into unmet clinical needs. LC screening to early detect malignant lung lesions in high-risk populations is not currently universally implemented and LC is detected at early stages only in a small proportion of patients. In this setting, a proper staging of the disease (especially mediastinal lymph nodes involvement), and the identification of patients at higher risk of local or distant recurrence after radical treatment are still critical issues for the optimal management of LC patients. In the metastatic setting, the development of innovative drugs and their introduction in clinical practice have increased the need for biomarkers predictive of treatment outcome and prognostic estimators (Bortolotto et al., 2021). To respond to this challenge, radiomic signatures have been extensively developed using data extracted from standard of care baseline CT and PET-CT images of both primary lung tumours and regional lymph nodes (Anan et al., 2022; Frix et al., 2021).

On the other hand, BC is the most incident tumour and the most common cause of cancer-related death among women (Sung et al., 2021). Although considerable progress has been made in BC through early diagnosis and improvement of treatment strategies, the heterogeneity of BC still holds many challenges in terms of non-invasive diagnosis, biomarker characterization (both through immunohistochemistry and genomics) and treatment personalization such as

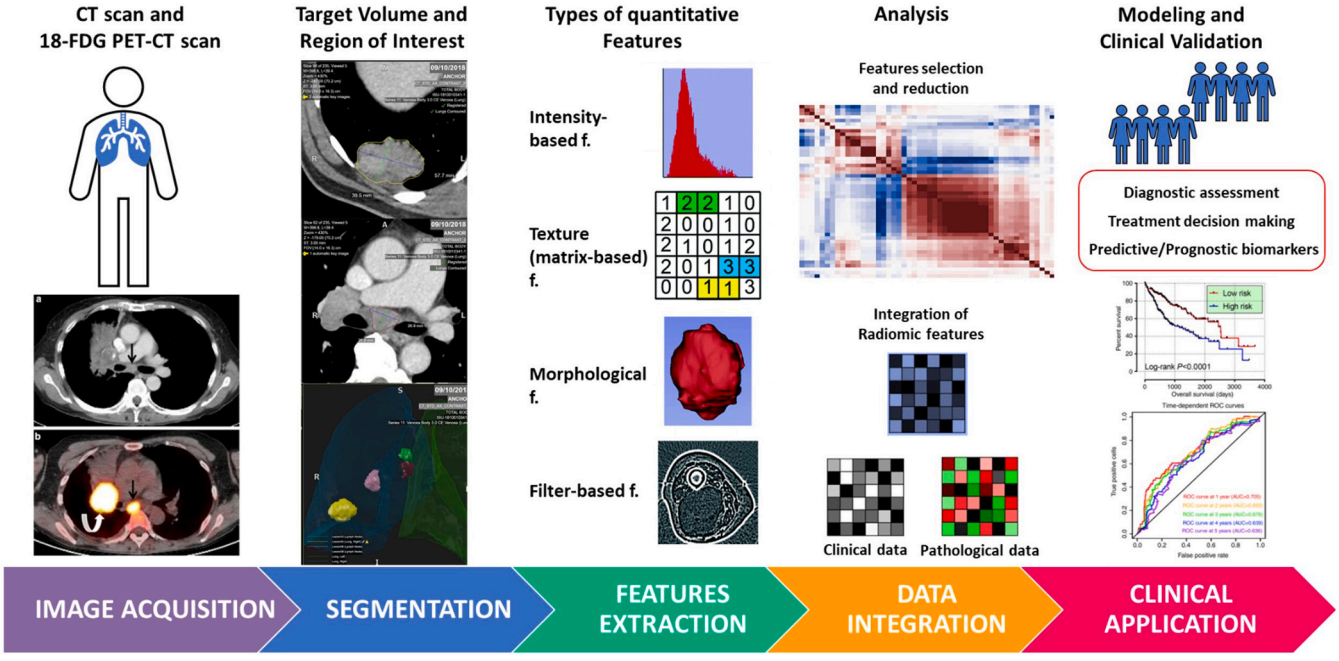

Fig. 1. The radiomics workflow. A schematic illustration of the radiomics pipeline including image acquisition and pre-processing, segmentation of the regions of interest, radiomic features extraction and selection and finally statistical modelling involving machine learning.

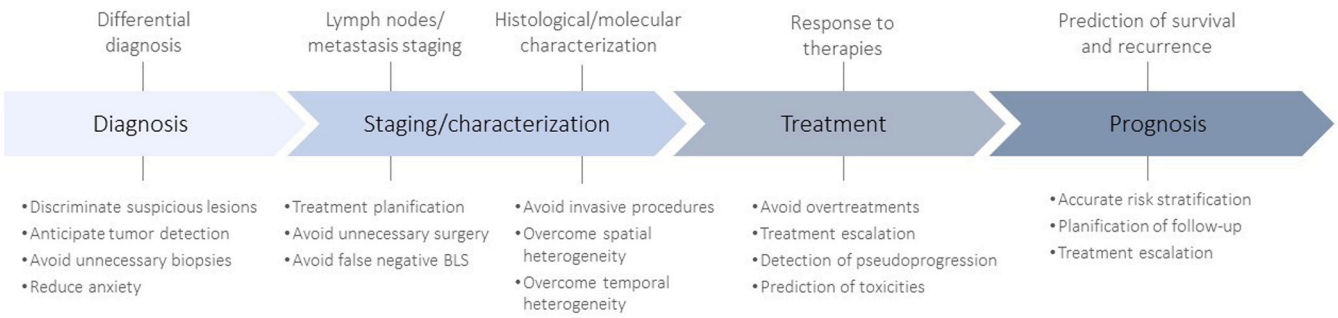

Fig. 2. Radiomic applications in clinical practice. Overview of potential clinical applications of radiomics in patients' history.

escalation or de-escalation. Breast MRI, which generates a large amount of anatomical and functional data, is frequently used in clinical practice for BC detection and is the most investigated method in breast radiomics (Granzier et al., 2020).

2.1. Screening

2.1.1. Lung

Several clinical trials have investigated the benefit of LC early detection through low dose computed tomography (LDCT). Two large clinical studies, the US National Lung Screening Trial (NLST) and the European NELSON trials, have showed a significant 20–24 % reduction in the risk of LC death with LDCT screening as compared to X-ray and no intervention, respectively (DR et al., 2011; $author1$ et al., 2020). Potential harms of LDCT screening to consider are false positive findings, overdiagnosis, cumulative radiation exposure and low cost-effectiveness. Indeed, the use of LDCT screening might lead to the detection of a large number of small nodules which will require a tissue biopsy to distinguish benign from malignant lesions.

In this context, radiomics can, first of all, be used to determine who is eligible for LC screening programs through the development of risk stratification models (ten Haaf et al., 2021): a model developed by Lu *et al.* identified smokers at high risk for incident LC and the area under the curve (AUC) was higher than that obtained using clinical eligibility requirements for screening (0.76 *vs* 0.63) (Lu et al., 2020). Moreover, segmentation of lung nodules and automatic volume estimation can be used to guide how the nodules are to be managed in accordance with international recommendations, Lung-RADS, created by the American College of Radiology (ACR) in 2014 and recently updated (Christensen et al., 2023). To enhance diagnostic efficiency, the computer-aided diagnosis (CAD) system was developed to support radiologists in the interpretation of medical images (Fujita, 2020).

DL-based CAD system can automatically recover and extract intrinsic features of a suspicious nodule. Multiple studies have demonstrated the effectiveness of radiomics in the early detection of malignant lung lesions: applying DL to LDCT, a 90 % sensitivity for pulmonary nodule identification has been achieved (Liu et al., 2020a; Balagurunathan et al., 2021). Chae *et al.,* in a study including 86 part-solid ground glass nodules, detected a combination of texture-based features to differentiate pre-invasive from invasive lung adenocarcinoma with an AUC of 0.981 (Chae et al., 2014). Using images and data from the NLST, it was shown that quantitative radiomics features may improve specificity (reducing false positives) in predicting malignancy status of pulmonary nodules when compared to size and shape (Balagurunathan et al., 2019). Moreover, examining the Lung Image Database Consortium and Image Database Resource Initiative (LIDC-IRDI) dataset, Kumar *et al.* proved the potential of radiomics in discriminating between malignant and benign lesions, with an accuracy of 79 %, a sensitivity of 78 % and a specificity of 76 % (Kumar et al., 2017). In another study, Liu *et al.* proposed a systematic methodology to qualify incidental pulmonary nodules based on observed radiological image traits: four feature signatures were found to be able to differentiate between malignant and benign nodules with an accuracy of 81 %, a sensitivity of 76 % and a specificity of 91 % (Liu et al., 2017). Furthermore, for pulmonary nodules requiring radiological follow-up, the assessment of changes in features (delta-radiomic) between baseline and follow-up scans can identify malignant lesions; moreover, some dynamic aspects, such as tumour doubling time, can be predicted by baseline scans (Huang et al., 2019, 2020).

In this context, radiomic models which can support the LC screening process have been developed: for example, Huang *et al.* presented a nomogram, including radiomic signatures from nodular and perinodular areas, which was capable of preoperatively differentiate invasive lesions from early-stage pre-invasive lesions of the lung (Huang et al., 2022).

2.1.2. Breast

While regular screening for BC is essential for early detection, the risk of false positives may cause unnecessary anxiety and interventions. In this context, radiomics may provide additional lesion-specific information to improve BC detection, decrease false positives and avoid unnecessary biopsies. Therefore, the use of radiomics applied to several radiologic techniques to discriminate between benign and malignant breast lesions has been evaluated.

The first studies, conducted on a small number of patients, explored the feasibility and the diagnostic performance of texture analysis of contrast-enhanced MRI (Gibbs and Turnbull, 2003; Holli et al., 2010) and dynamic contrast-enhanced (DCE)-MRI (McLaren et al., 2009; Nie et al., 2008; Wang et al., 2014) to differentiate benign and malign lesions.

Radiomics has also been applied in this setting to non-contrast enhanced MRI sequences, as for example diffusion-weighted imaging (DWI), with promising results (Vidić et al., 2018). Bickelhaupt et al. evaluated radiomics features from two unenhanced sequences (DWI and T2-weighted) in 50 patients with suspicious findings at screening mammography: a higher performance in distinguishing benign and malignant lesions was reported using radiomic features as compared to the use of mean apparent diffusion coefficient parameter alone (Bickelhaupt et al., 2017).

Moreover, in multiple studies, radiomics analysis based on various combinations of DCE-MRI, T2-weighted images and DWI proved high diagnostic performances, with AUC ranging from 0.805 to 0.984 (Hu et al., 2020; Parekh and Jacobs, 2020; Tsarouchi et al., 2020).

More recently, DL radiomics, using deep artificial neural networks, has been successfully applied in this field and proved to be more precise than analysis based on hand-crafted features (Antropova et al., 2017; Dalmiş et al., 2019; Jiang et al., 2021). Pötsch et al. investigated an automatic temporally and spatially resolved (4D) approach based on DCE-MRI: a high diagnostic ability in distinguishing between benign and malignant lesions was achieved (AUC of 83.5 %) as well as the potential for reducing the number of unnecessary biopsies (Pötsch et al., 2021).

Although less explored, radiomic approaches have also been applied

to mammography. For example, Wand et al. applied a radiomic model based on digital mammography to predict the malignant nature of suspicious masses, reaching an AUC of 0.934 in the training set and of 0.901 in the test set (Wang et al., 2022).

Recently, a meta-analysis of 19 studies (total of 5865 patients) confirmed the predictive value of radiomics, applied to MRI and/or mammography, to preoperatively diagnose BC: this metanalysis reported an integrated sensitivity, specificity and AUC of 0.84, 0.83 and 0.91, respectively (Li et al., 2022).

2.2. Histopathologic and molecular characterization

2.2.1. Lung

Nowadays, tumour biopsies are still the primary source of tissue for diagnostic purposes in LC and histology and molecular characterization drive the treatment algorithm in the advanced/metastatic setting, and more recently in the early-stage disease. LC is categorized into two main histological groups: small cell lung carcinoma (SCLC) and, more frequent, non-SCLC (NSCLC). With the emergence of high-throughput sequencing techniques, detailed molecular profiles of NSCLC have been identified: biomarker testing is essential to identify subgroups of NSCLC with oncogenic drivers that can be therapeutically targeted (Hendriks et al., 2023). Moreover, programmed death ligand-1 (PD-L1) expression by tumour cells assessed by immunohistochemistry remains up to date the most reliable predictive marker for immunotherapy response (Paver et al., 2021).

However, molecular profiling of the disease through tissue biopsies can be limited by the invasiveness of bioptic procedures as well as by tumour heterogeneity, which is rarely captured by small biopsies. In this regard, it has been investigated whether radiomics could provide an image-based phenotypic characterization of the lesion. In a study by Liu *et al.*, the authors investigated the association between radiomics features and tumour histological subtypes, establishing a nomogram to classify lesions as SCLC or NSCLC: in the validation set, a logistic regression nomogram – integrating radiomics signatures and clinical factors - was able to distinguish between different LC histological subtypes with an AUC of 0.94 and an accuracy of 86 % (Liu et al., 2020b). Moreover, a LASSO logistic regression model was developed to discriminate between adenocarcinomas and squamous cell carcinomas: the performance of the radiomic signature in the validation cohort showed an AUC of 0.89 with a sensitivity of 82 % and a specificity of 90 % (Zhu et al., 2018). In addition, Wu *et al.* identified a 53-feature radiomic signature allowing for the prediction of LC histology with an AUC equal to 72 % in an independent external validation cohort treated at a different centre (Wu et al., 2016a). Similar results were also obtained using three machine learning (ML) classifiers: naive Bayes (NB), k-nearest neighbours (KNN) and radial basis function-based (RBF) artificial neural network. Using those classifiers, in the validation cohort, radiomics-based features were able to detect histopathological patterns with an AUC of 0.81 (Ferreira Junior et al., 2018).

Quantitative features have also been used to recognize the presence of specific mutations and gene alterations: the radio-genomic analysis of NSCLC allows for the identification of biomarkers that reflect cellular and molecular characterization and which might serve as surrogates to non-invasively identify molecularly defined features (Zhou et al., 2018; Anagnostopoulos et al., 2022). Most studies investigated the potential use of radiomics to differentiate EGFR/ALK/ROS1-positive and -negative lung adenocarcinomas. Using data from 844 lung adenocarcinoma patients with pre-operative CT images, Wang *et al.* identified a DL model achieving promising predictive performance in both the primary cohort (AUC=0.85) and in an independent external validation cohort from a different hospital (AUC=0.81): the DL score showed significant differences in *EGFR*-mutated and *EGFR*-wild type adenocarcinomas ($p<0.001$) (Wang et al., 2019). Rios Velazquez *et al.*, in a dataset of 381 lung adenocarcinoma patients, also found a radiomic signature that successfully discriminated between *EGFR*-mutated and *EGFR*-wild type cases with an AUC of 0.69. Interestingly, combining this signature with a clinical model predicting *EGFR* status, the prediction accuracy significantly improved (AUC=0.75) (Rios Velazquez et al., 2017). Another study by Zhang *et al.* reported a multivariate analysis, including seven handcrafted radiomic features and three clinical features, that was of capable of predicting *EGFR* status in 180 LC cases with an AUC of 0.87 (Zhang et al., 2018). Moreover, one study by Zhao *et al.* provided a radiomics score based on 11 radiomics features calculated for each lesion, that integrated with clinical model was able to predict not only the mutational status of *EGFR* but also the type of alteration (exon 19 deletion and exon 21 L858R mutations): the respective AUC values in the validation cohort were 0.73 and 0.76 (Zhao et al., 2020).

Furthermore, in a study conducted in 539 NSCLC patients, the authors assessed clinical and radiomics variables extracted from PET/CT and CT-scan aiming to investigate the potential role of radiomics to differentiate ALK/ROS1/RET fusion-positive and fusion-negative lung adenocarcinomas: using seven features, they built a prediction model that resulted in 73 % sensitivity and 70 % specificity (Yoon et al., 2015). Subsequently, Choe *et al.*, using a dataset of 503 patients, proposed a two-level stepwise binary radiomics-based classification model to diagnose ALK status, obtaining a diagnostic performance of the intratumoral radiomic model with an AUC of 0.77 and 0.68 for the development and validation sets, respectively (Choe et al., 2021).

PD-L1 expression represents a crucial predictor in selecting patients for immunotherapy, both in advanced stage and in localized disease. Indeed, in stage III NSCLC patients undergoing definitive chemoradiation therapy (CRT), the use of consolidation therapy with durvalumab is limited to PD-L1 positive patients (Paz-Ares et al., 2020). PD-L1 expression evaluation is currently based on pre-treatment tissue sample, which does not reflect changes in the tumoral microenvironment after CRT, as concordance between PD-L1 expression of diagnostic biopsy and surgical specimen after CRT is variable (Pavan et al., 2022).

In a study including 390 NSCLC patients, Sun *et al.* reported that PD-L1 positivity could be predicted using a model that combines a radiomics signature and clinico-pathological characteristics, resulting in AUC of 0.83 and 0.85 in the training and validation cohort, respectively (Sun et al., 2020). Moreover, Shao *et al.* presented a multi-label multi-task DL system to non-invasively predict driver mutations and PD-L1 expression utilizing routine CT imaging. This radiogenomic model integrated transformer-based DL features and radiomic features from CT imaging from 1096 LC patients: the system achieved an AUC of 0.862 in discriminating the mutational status of a panel of 8 genes (including EGFR, ALK, ERBB2, BRAF, MET, ROS1, RET and KRAS) and 0.868 in classifying PD-L1 expression, respectively (Shao et al., 2022).

2.2.2. Breast

BC is an extremely heterogenous disease and, considering the different clinical behaviour and treatment sensitivity, an accurate characterization of histopathological and genomic features is crucial.

Different studies have evaluated the ability of radiomics to predict commonly used BC biomarkers (such as hormone receptor [HR] status and HER2) in a non-invasive manner. Indeed, in order to overcome tumour heterogeneity and to avoid invasive procedures before surgery, radiomics has been evaluated as an alternative to diagnostic biopsies in predicting BC subtypes. Using diffusion-weighted MRI, Ni et al. reached an overall accuracy of 96.4 % for predicting the histopathological subtypes of BC in 112 patients (Ni et al., 2020). Similarly, Ki67 is a key prognostic factor in BC, especially in early HR+/HER2- BC, and is commonly used as a clinical surrogate to differentiate between luminal A and luminal B subtypes. The ability of radiomics to predict Ki67 evaluation by IHC in the primary tumour has therefore been explored in several studies (Jiang et al., 2022; Kayadibi et al., 2022; Zhang et al., 2020). The largest study by Liu et al., including 328 patients, analysed different MRI sequences that were combined in a multiparametric model which reached an AUC of 0.888 (Liu et al., 2021).

Furthermore, BC can be stratified into four molecular intrinsic

subtypes (luminal A, luminal B, HER2-enriched and basal like) according to gene expression patterns, even though in clinical practice an immunohistochemistry surrogate is most commonly used (Sørlie et al., 2001). Given the costs and the limited availability of genomic analyses, a radiomic approach to predict BC intrinsic subtypes appears particularly appealing and has been explored. Although limited by the use of different radiomics techniques, a meta-analysis of 41 studies for a total of 10.900 patients has highlighted that radiomics can be used to stratify BC into the four intrinsic subtype subgroups with a good performance (AUC above 80 %). However, a relevant variability was observed among different subtypes and different studies, highlighting the need for further standardization (Davey et al., 2021a).

Beyond molecular subtypes, gene expression assays have also been implemented to improve prognostic stratification of early HR+/HER2- BC and to guide adjuvant treatment choice (Kalinsky et al., 2021; Sparano et al., 2018). However, the routinary use of these tests may be limited by costs and execution time. Different studies have therefore assessed the potential use of breast MRI radiomics to predict genomics assay results, in particular Recurrence Score (RS) as assessed by the Oncotype DX assay. Davey et al. performed a meta-analysis of 9 studies: a high sensitivity of 0.89 was reported in identifying tumours with low risk (RS<18) compared to tumours at intermediate-high risk (RS≥18), while sensitivity was lower (0.79) in discriminating high risk tumours (RS≥30) compared to the low-intermediate risk (RS<30) (Davey et al., 2021b). Additionally, another study evaluated the association between MRI radiomics and various genomic assays (Oncotype DX, MammaPrint and PAM50) in a retrospective series of 84 patients. Radiomics distinguished low and high risk of recurrence categories with AUC values of 0.88, 0.76 and 0.68 for MammaPrint, Oncotype DX, PAM50, respectively (Li et al., 2016).

2.3. Staging

2.3.1. Lung

2.3.1.1. Localized disease. Non-invasive biomarkers that are able to capture tumour burden could offer additional information to aid decision-making process in precision medicine. The identification of mediastinal lymph node involvement represents a crucial information for cancer staging and treatment choice in early and locally advanced stage NSCLC. In this context, radiomic signatures based on CT scan features of the primary tumour have been reported to quantitatively and non-invasively predict occult mediastinal lymph node metastasis in lung cancer patients (Yang et al., 2018; Zhong et al., 2018). Also, a PET/CT nomogram, incorporating a radiomic-based score and SUVmax, has been reported to improve the diagnostic performance for nodal metastasis: Xie *et al.* retrospectively analysed 263 pathologically confirmed lymph nodes from 124 patients with NCSLC building radiomics scores from malignancy-related features, such as SUVmax, short-axis diameter, and CT radiomics features extracted from the ROI of lymph nodes based on PET/CT. These radiomics scores were significantly associated with nodal status in both the training cohort with AUC of 0.849 and the testing cohort with AUC of 0.828 (Xie et al., 2021). However, few studies have extracted radiomics features from mediastinal lymph nodes segmentation and confirmed that combining textural and shape features from both the primary tumour and the regional lymph nodes could provide essential information, in addition to that offered by assessing the primary tumour site alone, in predicting their involvement (Bayanati et al., 2015; Andersen et al., 2016; Coroller et al., 2017). At this regard, Dong et al. built a model to estimate mediastinal lymph nodes neoplastic involvement based on preoperative contrast-enhanced CT imaging: among six ML methods assessed, a logistic regression model including the eight strongest features showed a significant association with mediastinal lymph nodes status and a satisfactory diagnostic performance for distinguishing malignant lymph nodes from benign lymph nodes (Dong et al., 2021). In addition, multivariate models based on radiomic signatures, clinical characteristics and haematological parameters have been reported to predict lymph nodes involvement with a better performance than imaging alone (Chen et al., 2022).

2.3.1.2. Metastatic disease. Radiomic studies have shown that image-based models have the potential to complement disease staging also in the metastatic setting. Wu *et al.* reported that a radiomic-based feature predicted the presence of metastases in early-stage lung cancer using a Cox proportional hazards regression model (AUC=0.71) (Wu et al., 2016b). Similarly, Coroller *et al.*, in a study performed on 182 cases of lung adenocarcinoma, built a combined model of radiomic and clinical features to predict the presence of distant metastases (AUC=0.61) (Coroller et al., 2015). In another study, computed-tomography (CT) imaging features from peritumoral tissues were proved to be significantly associated with distant metastases in locally advanced NSCLC (p-value < 0.05) (Dou et al., 2018). In particular for brain involvement, Cong *et al.* developed a radiomics model using CT images acquired at first diagnosis to estimate the risk of occult brain metastases in patients with stage IV LC: by incorporating a radiomics signature and clinical risk factors, the authors built a nomogram that achieved optimal performance, showing high agreement between the actual occult brain metastases probability and the probability predicted by the nomogram (p=0.427) (Cong et al., 2021).

2.3.2. Breast

Axillary lymph node status is essential in BC staging, prognostic assessment, and treatment planning. In patients with early BC and clinically negative lymph nodes, sentinel lymph node biopsy is the current standard method to assess nodal status. However, complications such us lymphedema, infections and paraesthesia have been reported (Lucci et al., 2007), as well as the possibility of false negative results (Krag et al., 2007). To overcome these limitations, radiomics has been proposed as a potentially more precise non-invasive tool for preoperative axillary staging.

The ability of radiomics to predict sentinel lymph node involvement was first evaluated by Dong Y. et al. in 146 patients: the combination of radiomic analysis of T2-FS and DWI-MRI reached an AUC of 0.863 in the training set and an AUC of 0.805 in the validation set (Dong et al., 2018). Similar results with an AUC of 0.83 were also obtained by Liu et al. applying radiomics and automatic ML to DCI-MRI (Liu et al., 2019a).

The integration of clinicopathologic characteristics of the primary tumour to the radiomic model further improved its performance in various independent studies, both when taking into account DCE-MRI and fat-suppressed T2-MRI sequences (Liu et al., 2019b; Qiu et al., 2022; Wang et al., 2021).

Despite many encouraging results from retrospective mono-institutional cohorts (Cattell et al., 2022; Yang et al., 2021; Zhu et al., 2021), data from only one prospective trial is currently available: Liu M. et al. evaluated DCE-MRI of 164 patients and proposed a model incorporating radiomics features and pharmacokinetic parameters extracted by hemodynamic characteristics which reached an AUC of 0.80 (Liu et al., 2020c).

Recently, the diagnostic performance of DCE-MRI in predicting axillary lymph node involvement was further confirmed by a meta-analysis of 13 studies: a pooled sensitivity of 0.82 (95 % CI 0.75–0.87), a specificity of 0.83 (95 % CI 0.74–0.89) and an AUC of 0.89 (95 % CI 0.86–0.91) were reported, although limited by the heterogeneity of the studies analysed (Zhang et al., 2022a).

2.4. Treatment outcome

2.4.1. Lung

AI has a potential role in clinical decision making by predicting treatment response, adverse events, and survival outcomes (Echle et al.,

2021). The use of radiomics in predicting response to therapy was explored by several research groups in order to adapt treatment strategies individually and allow a personalized medicine. In the context of early-stage disease, Coroller *et al.* studied radiomics data derived from pre-treatment images of locally advanced NSCLC patients to predict pathological response after neoadjuvant CRT. This study showed that seven radiomic features were predictive of residual disease (AUC=0.6) and one radiomic feature was predictive of complete response (AUC=0.63) (Coroller et al., 2017). In the advanced setting, Dercle *et al.* retrospectively analysed data from the prospective clinical trials CheckMate017 NCT01642004, CheckMate063 NCT01721759 and NCT00588445: radiomics signatures were derived from quantitative analysis of tumour changes from baseline to first on-treatment assessment and the AI model based on a random forest algorithm. The radiomic features predicted the disease sensitivity to nivolumab with an AUC of 0.77, to docetaxel with an AUC of 0.67 and to gefitinib with an AUC of 0.82 (Dercle et al., 2020). Focusing on distinct treatment options, in a retrospective study conducted on *EGFR*-mutated NSCLC patients, a deeply learned score (DLS) was developed using PET/CT images to identify patients most likely to benefit by tyrosine kinase inhibitors: a higher EGFR-DLS ($\geq$0.5) significantly predicted a longer progression-free survival (PFS) compared to the lower EGFR-DLS ($<$0.5) group (hazard ratio [HR]: 0.24, p$<$0.001) (Mu et al., 2020a). Moreover, a similar study was conducted to identify a CT-based radiomics signature predictive of better outcome in 63 *ALK*-rearranged NSCLC patients treated with crizotinib: the authors presented a radiomic model of three features that showed a good performance for PFS prediction, with an AUC of 0.82 (Li et al., 2020). In addition, Zheng *et al.*, using data from 558 SCLC patients, developed a radiomic nomogram based on baseline CT scans to estimate PFS. A radiomic signature was created, using 6 CT-based radiomic features, and was significantly associated with PFS (p $<$ 0.001). Incorporating this radiomic signature into a nomogram resulted in better performance for PFS estimation than the clinical nomogram alone, as well as better prediction of PFS at 6 months and 12 months with an AUC of 0.885 and 0.846, respectively (Zheng et al., 2023a). Regarding the prediction of response to immunotherapy, a recent meta-analysis confirmed the potential usefulness of radiomic features in monitoring therapeutic response beyond traditional morphologic and metabolic criteria; however, most of the studies were characterized by poor methodological quality and scarce reproducibility (Chen et al., 2021). Furthermore, the identification at baseline of patients with NSCLC most likely to present adverse events (AEs), in particular immune-related AEs, can optimize treatment planning. In a retrospective study including 146 NSCLC patients who were treated with immune checkpoint blockade, radiomic features extracted from pre-immunotherapy CT and PET/CT scans were used to generate a radiomic score. This radiomic signature was able to predict patients with and without immune-related AEs with an AUC of 0.88 in a prospective independent validation cohort (Mu et al., 2020b).

2.4.2. Breast

Neoadjuvant chemotherapy (NACT) has become the standard of care for many early/locally advanced BCs (Miglietta et al., 2021; NCCN Clinical Practice, 2021). However, response to NACT is extremely variable and, despite rare, disease progression during NACT remains a challenging scenario (Caudle et al., 2011; Cortazar et al., 2014). Moreover, early evaluation/prediction of treatment response, such as pathological complete response (pCR) or residual disease, might enable treatment escalation/de-escalation during NACT therefore improving treatment personalisation.

The ability to predict pCR using pre-treatment MRI has been investigated in several studies. Cain et al. evaluated a large cohort of 288 patients and developed an independent predictive model based on radiomic features able to predict pCR with higher accuracy in the triple negative/HER2-positive subgroup (Cain et al., 2019). Similarly, Braman et al. evaluated the combination of intratumoral and peritumoral radiomic features from DCE-MRI, showing that the performance of this method varied according to BC subgroups, thus highlighting the need for incorporating clinicopathological parameters in the radiomics models (Braman et al., 2017). Similar results were also observed by Zhang et al. applying a radiomic approach to contrast-enhanced spectral mammography, reaching an AUC of 0.906 in the training dataset and of 0.790 in the test dataset (Zhang et al., 2023). Additionally, few studies have evaluated the ability of DL in predicting response to NACT and a recent metanalysis reported a higher accuracy of this method compared to ML on MRI (Liang et al., 2022).

Moreover, in this context, quantitative perfusion parameters have been reported to describe changes in cell density and tumour perfusion (Jun et al., 2019; Tudorica et al., 2016). Different studies have applied artificial intelligence to the comparison between pre-treatment MRI and early post-treatment MRI, and pharmacokinetic parameters from DCE-MRI consistently proved to be one of the most sensitive methods to predict early response (Machireddy et al., 2019; Tahmassebi et al., 2019; Thibault et al., 2017).

2.5. Prognosis

2.5.1. Lung

Concerning the prognostic potential of radiomic models, in a retrospective study evaluating pre-operative CT-scan of 800 LC patients, a DL survival model was trained to extract prognostic information: they generated a Cox regression model combining the model outputs and other clinical features that proved to independently predict disease-free survival (external validation set: HR= 3.6; p =0.003) (Kim et al., 2020a). Moreover, in 2018, Hosny et al. conducted a study including 1194 patients with NSCLC and identified a prognostic signature based on CT-scan data, which used a three-dimensional convolutional neural network (CNN) to predict survival of patients treated with radiotherapy and surgery: the authors showed that the predictions of the CNN model were significantly associated with 2-year OS from first treatment with radiotherapy (AUC =0.70) or surgery (AUC =0.71) patients (Hosny et al., 2018). Furthermore, Tang *et al.* correlated pre-treatment radiomic features to the tumour immune phenotype in stage I-III NSCLC patients: they developed an immune pathology-informed model that classified patients into 4 clusters using radiomics features and demonstrated that patients included in the cluster with low PD-L1 and high CD3 cell count had better prognosis (Tang et al., 2018). Recently, in the same setting (stage I-IIIB NSCLC), Zheng *et al.* investigated the value of preoperative CT features and clinical features in predicting prognosis after radical resection: using 4 selected features, the radiomics signature showed a favourable discriminative performance for prognosis, with an AUC of 0.91; moreover, the authors developed a nomogram, which combined radiomic signature, N stage and tumour size, that exhibited good prognostic ability with a C-index of 0.91 for OS (Zheng et al., 2023b). In addition, Le *et al.,* analysing 577 NSCLC patients, proposed a risk score model whose performance as a prognostic indicator was superior to other clinical indicators (age, stage and gender). Patients were stratified based on predicted survival using a risk score based on 10 radiomics signatures: in the external independent validation set, this risk score was able to predict 1, 3, and 5 years survival with an AUC of 0.676, 0.629 and 0.709, respectively (Le et al., 2021). More recently, Hou *et al.* collected pre-treatment CT images and clinical data of around 500 patients diagnosed with NSCLC (all stages) which was analysed using a deep neural network. Through this methodology, they developed a survival prediction model that combined eight radiomic features and five clinical features which outperformed prediction models based only on radiomic or clinical features. The C-index values of the combined model was 0.74, 0.75, and 0.75 at 8, 12, and 24 months after diagnosis, respectively; and AUC values were 0.76, 0.74, and 0.73, respectively (Hou et al., 2022). Finally, in a prospective study conducted on two independent cohorts of 262 and 50 node-positive NSCLC patients, PET information demonstrated to have higher prognostic value when

extracted from metastatic lymph nodes, as compared to primary tumour alone, further complementing its information (Carvalho et al., 2018).

2.5.2. Breast

Radiomics has also been applied to the prediction of long-term outcome of BC patients to improve risk stratification and potentially guide treatment decisions.

Tumour heterogeneity, as assessed by radiomic MRI based features, has been reported to be associated with disease recurrence and overall survival in patients with early or locally advanced BC (Eun et al., 2021; Kim et al., 2017), and this type of approach has been more extensively explored in the triple-negative BC subtype (Cheng et al., 2021; Kim et al., 2020b; Aw Yong et al., 2020).

To further refine outcome prediction, radiomics signatures have been integrated in nomograms with clinicopathological features. In particular, Park. et al. incorporated radiomic signature, MRI findings, and clinicopathological findings of 294 patients and developed a nomogram able to predict DFS better than clinicopathological and radiomic features alone (Park et al., 2018).

3. Future perspectives

In the era of precision therapy, radiomics has attracted growing interest for its potential in identifying new non-invasive tumour biomarkers, becoming a new translational field of oncology. Indeed, cancer radiomics holds unprecedented opportunities to enhance decision-making process for cancer patients and presents many unique strengths and potentials as a complementary tool for further personalization of cancer care.

As we here reviewed for LC and BC, radiomics may be applicable throughout several key steps of a cancer patient management, such as screening, diagnosis, treatment, and prognostic assessment. A similar wide approach has also been reported in other types of cancer, confirming its transversal use throughout different organs and different imaging techniques (Caruso et al., 2021a, 2021b). Histologic assessment through invasive biopsies still represents the gold standard for cancer diagnosis and tumour characterization. Nonetheless, intrinsic limitations related to limited representativity of samples and accessibility of certain lesions, and risks related to the use of invasive techniques are inevitable. Radiomics could therefore guide the site of biopsy, as well as provide further and rapidly available biological information, overcoming spatial heterogeneity and avoiding unnecessary procedures. Furthermore, the non-invasiveness and safety of radiological imaging could allow for repeated monitoring of tumoral features throughout a patient's clinical history, thus overcoming temporal heterogeneity (Parekh and Jacobs, 2016).

Beyond biological characterization, radiomics could also improve early tumour detection by identifying subtle imaging features, that might be overlooked in standard evaluations, and which are crucial for initiating timely interventions and improving survival rates. Furthermore, radiomics holds great potential for cost-effectiveness in oncology. By maximizing the utility of existing imaging, it could reduce the need for additional, often invasive, procedures, such as biopsies and exploratory surgeries. This not only minimizes patient discomfort and risks, but also leads to more efficient resource allocation within healthcare systems. Additionally, the early detection of signs of treatment effectiveness or resistance allows for timely modification and adaptation of therapeutic strategies, enhancing the precision and efficacy of oncological care.

However, future challenges must be addressed before bringing radiomics into daily clinical practice, especially in terms of standardization and validation of many steps within its workflow. In order to successfully integrate radiomics in the decision-making processes, standardized models applied to settings consistent with real-world clinical practice, ideally validated in multicentric prospective trials, are needed. Lack of standardization in acquisition (related to difference in acquisition parameters and type of machines), segmentation (manual, semi-automatic, automatic), feature selection (unsupervised or supervised) and processing, as well as in treatment protocols, represents one of the main challenges. Despite considerable improvement in automatic segmentation and classification led by ML and DL, a consistent variability still persists among different studies. The performance of these approaches also widely depends on the quality of the training set and supervised algorithms still hold a better power compared to unsupervised ones (Litjens et al., 2017; Martín Noguerol et al., 2019). Low reproducibility and consequent difficulties in outcome comparison and replicability are therefore some of the main limits in radiomics applicability (Zhang et al., 2022b). Moreover, most of the published studies have assessed retrospective single institute datasets, splitting them in a training cohort, which is used to develop a new model, and a validation cohort, which is used to evaluate the performance of the proposed method. This widely used method might potentially led to the development of several alternative radiomic models, including different combinations of radiologic features, for the same clinical setting, depending on how the dataset is randomly split. Additionally, the reproducibility of radiomics studies is often limited by the frequent use of internal validation cohorts, which are susceptible to over-fitting. As highlighted throughout the review, only a limited number of studies employed external validation cohorts, providing more robust and valuable validations. As a possible solution to some of the main issues invalidating radiomics studies, radiomic objectives should be included in the design of prospective interventional trials, in order to standardize image acquisition protocols and the development of radiomic models. Moreover, multicentric validations testing the stability of a radiomic model should be performed (Castello et al., 2022).

For what concerns repeatability and reproducibility, several recent guidelines have been proposed to encourage detailed description of radiomic workflow and to provide a guide for the development of radiomic models (Liu et al., 2019a; Kalpathy-Cramer et al., 2014; Collins et al., 2015). Furthermore, some criteria have been suggested for validating radiomic studies: for instance, the radiomic quality score (RQS), based on 16 items ranging from acquisition parameters to data sharing, has been proposed to improve the quality of radiomic research (Lambin et al., 2017b). Radiomic software standardization is also useful as it could guarantee that the same feature values are extracted from the same image when using different softwares (McNitt-Gray et al., 2020). More recently, the CheckList for EvaluAtion of Radiomics research (CLEAR) has been proposed as a standardized tool to improve the repeatability and reproducibility of radiomics research. This 58-item checklist aims to provide a comprehensive framework for designing and reporting a radiomics study and has been endorsed by the ESR Executive Council and EuSoMII (Kocak et al., 2023). Finally, data-sharing must be encouraged: anonymized databanks accessible across different institutions could allow for the integration of small datasets into bigger datasets, which might allow for external validation of radiomic models in settings similar to the real-world (Kundu et al., 2022).

In the era of biomarker-driven treatments, both in LC and BC, there are several unmet needs still poorly explored by radiomics. In the future, radiomics could help selecting patients who can benefit from loco-regional treatments, such as surgery or radiation therapy. In this context, few preliminary data assessing the possibility of predicting response to radiotherapy in stage III NSCLC using longitudinal CT radiomics features are available: for example, Zhang *et al.* considered 10 NSCLC patients and, by assessing selected radiomic features extracted from ROI, was able to predict trends in tumour change and the moment of greatest change during radiotherapy (Zhang et al., 2021a). Recently, a model to predict cancer resistance to radiation (Lewis and Kemp, 2021). Radiomics has been applied to pre-surgical evaluation too: features extracted from baseline images can be used to predict recurrence after surgery, and could help in identifying high risk patients who could be suitable to receive adjuvant chemotherapy (Jones et al., 2021). Furthermore, prediction of ICI effectiveness (beyond PD-L1 expression)

is still a challenge (in both LC and BC), and quantitative image analysis carries a great potential in capturing intra- and inter-lesion heterogeneity and changes in tumour microenvironment (TME) (Zhang et al., 2021b). Yoon *et al*. demonstrated the potential of radiomic features as non-invasive biomarkers to assess TME of NSCLC, showing a relationship between radiomic features and Th2 cell signatures in a training set of 89 NSCLC patients (Yoon et al., 2020).

While most studies focused on early or locally advanced disease, the characterization of metastatic lesions is still underexplored. Considering the variability of biomarkers expression between primary tumours and secondary lesions, radiomics could help identify tumour biomarkers as well predict response to systemic treatments and radiotherapy. He et al. reported the performance ability of CT-based radiomics in predicting the efficacy of anti-HER2 therapy in patients with liver metastases from BC, underling the potential of radiomics in the choice of treatment algorithm and personalized therapies (He et al., 2022). Similarly, the ability of radiomics in differentiating between primary tumours or metastases and in the identification of the tumour of origin in patients with metastases from unknown primary site seems promising but still poorly investigated. In the field of neuro-imaging, a high succession rate was reported in differentiating between glioblastoma and solitary brain metastasis through T1 weight MRI, while Kneip et al. reported the feasibility of discriminating primary tumour histology in patients with brain metastases of unknown origin (Kniep et al., 2019).

4. Conclusions

In the last decades, developments in radiological imaging have deeply changed cancer care and oncology practice. More recently, combining the improving resolutions of images and recent advances in technologies, computerized analysis has allowed to capture anatomical and functional features and to analyse them through ML and DL algorithms. Despite being a relatively recent discipline, radiomics has been increasingly investigated in many clinical settings and a huge amount of data has consistently shown its promising potentialities. Indeed, radiomics can be integrated at multiple points in clinical practice and serve as a fundamental tool in precision oncology, ultimately enhancing the ability to deliver personalized, effective, and timely cancer care. However, further improvements in terms of standardization and prospective validation are still required to overcome current limitations and to allow the transition of radiomics toward clinical applications as a key player in precision medicine.

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CRediT authorship contribution statement

Alessandra Ferro, Michele Bottosso: Conceptualization, Data curation, Methodology, Writing – review & editing. **Gaia Griguolo, Giulia Pasello**: Conceptualization, Funding acquisition, Supervision, Validation, Writing – review & editing. **Maria Vittoria Dieci, Valentina Guarneri**: Conceptualization, Supervision. **Elena Scagliori, Federica Miglietta, Vittoria Aldegheri, Laura Bonanno, Francesca Caumo**: Data curation, Investigation, Visualization.

Declaration of Competing Interest

AF reports advisory boards/honoraria/speakers' fee/consultant from BMS, MSD, Roche; MVD reports personal fees for consultancy/advisory role from Eli Lilly, Pfizer, Novartis, Seagen, Gilead, MSD, Exact Sciences, AstraZeneca, Roche, Daiichi Sankyo, Roche; FM reports fees from Roche, Novartis, Seagen, Pfizer, Lilly, Gilead and MSD; LB reports speaker fee/advisory board: Astra-Zeneca, MSD, BMS, Roche, Novartis, Lilly; steering committee and coordinating PI: Astra-Zeneca; local PI: Astra-Zeneca, Roche, MSD, BMS, Janssen, Pharmamar, OSEimmunotherapeutics; unconditioned research support: Astra-Zeneca; VG reports personal fees for advisory board membership for AstraZeneca, Daiichi Sankyo, Eisai, Eli Lilly, Exact Sciences, Gilead, Merck Serono, MSD, Novartis, Pfizer, Olema Oncology, Pierre Fabre; personal fees as an invited speaker for AstraZeneca, Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, GSK, Novartis, Roche and Zentiva; personal fees for expert testimony for Eli Lilly; GG reports personal fees as invited speaker from Eli Lilly, Novartis and MSD, advisory boards for Gilead, Seagen and Menarini; GP reports advisory boards/honoraria/speakers' fee/consultant from Amgen, AstraZeneca, BMS, Eli Lilly, Jansenn, MSD, Novartis, Roche and unconditioned research support From AstraZeneca, Roche, MSD. The remaining authors declare no competing interests.

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