European Journal of Radiology Open 11 (2023) 100511

Contents lists available at ScienceDirect

European Journal of Radiology Open

journal homepage: www.elsevier.com/locate/ejro

Delta-radiomics in cancer immunotherapy response prediction: A systematic review

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ARTICLE INFO

Keywords:
Delta radiomics
Immunotherapy
Radiomics
Oncology
Therapy response evaluation
Radiomics quality score

ABSTRACT

Background: The new immunotherapies have not only changed the oncological therapeutic approach but have also made it necessary to develop new imaging methods for assessing the response to treatment. Delta radiomics consists of the analysis of radiomic features variation between different medical images, usually before and after therapy.

Purpose: This review aims to evaluate the role of delta radiomics in the immunotherapy response assessment.

Methods: A systematic search was performed in PubMed, Scopus, and Web Of Science using "delta radiomics AND immunotherapy" as search terms. The included articles' methodological quality was measured using the Radiomics Quality Score (RQS) tool.

Results: Thirteen articles were finally included in the systematic review. Overall, the RQS of the included studies ranged from 4 to 17, with a mean RQS total of 11,15 ± 4,18 with a corresponding percentage of 30.98 ± 11.61 %. Eleven articles out of 13 performed imaging at multiple time points. All the included articles performed feature reduction. No study carried out prospective validation, decision curve analysis, or cost-effectiveness analysis.

Conclusions: Delta radiomics has been demonstrated useful in evaluating the response in oncologic patients undergoing immunotherapy. The overall quality was found law, due to the lack of prospective design and external validation. Thus, further efforts are needed to bring delta radiomics a step closer to clinical implementation.

1. Introduction

1.1. Immunotherapy

Immunotherapy revolutionized the field and brought attention to new opportunities toward precision medicine [1]. Cancer immunotherapy aims to reactivate a pre-existing stalled immune response or to elicit a de novo immune response [2]. Indeed, cancer cells send molecular signals to prevent the immune system from attacking them [3]. In particular, T cells are negatively modulated with different checkpoint pathways and allowing for continued tumor growth.

With the advent of new immunotherapies, the treatment paradigm in most malignancies has completely changed in the last 10–15 years. Immune checkpoint inhibitors (ICIs) can inhibit molecules produced by cancer cells that negatively regulate the immune response. The major targets of ICIs are anticytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and anti-programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) which are overexpressed on different types of cancer. These types of drugs have also achieved satisfactory results in patients with advanced cancer [4].

Abbreviations: CTLA-4, Cytotoxic T-lymphocyte-associated antigen 4; PD-1, Programmed cell death protein 1; PD-L1, Programmed cell death ligand 1; RECIST, Response assessment criteria in solid tumors; RQS, Radiomics Quality Score; NSCLC, non-small-cell lung cancer.

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https://doi.org/10.1016/j.ejro.2023.100511
Received 10 May 2023; Received in revised form 11 July 2023; Accepted 12 July 2023

Additionally, new immune control molecules are emerging such as the Ig domain V suppressor of T cell activation also called PD-1 homolog and ectonucleotidases that belong to the ribosyl cyclase family, which are giving promising results [5].

To date, biopsy is necessary to identify the presence of immunotherapy targets. However, tissue biopsy is invasive and limited to a restricted portion of the tumor, therefore not addressing the temporal and spatial heterogeneity of the tumor [6,7].

For obtaining a personalized treatment based on the phenotypic and genomic changes of the tumor over time, it is necessary to find reliable biomarkers that objectively reproduce these tumoral changes over time, easily obtainable and reproducible. In an oncological setting, it is advisable to modulate the therapeutic choices based on tumor variability, trying to prevent and predict the development of resistant tumor clones.

1.2. Imaging state of the art and limits in immunotherapy drugs scenario

Oncological imaging plays a pivotal role in the assessment of therapy response [8].

In 2000, response assessment criteria in solid tumors (RECIST) were introduced by an international working group. These criteria are aimed to standardize and simplify tumor response criteria [9], including definitions of the minimum measurable lesion size, instructions on how many lesions to follow and the use of one-dimensional measures for assessing overall tumor burden [9]. The RECIST criteria has subsequently been widely accepted, but with rapid technological innovations in imaging techniques, their revision has become necessary [10].

The main imaging-related changes in RECIST 1.1 were overall the number of target lesions, the assessment of pathological lymph nodes, a better definition of disease progression, a better definition of the unequivocal progression of non-target lesions and finally the inclusion of 18F-FDG PET in the detection of new lesions [10].

The introduction of new therapeutic options, such as immunotherapy, has changed the scenario.

In the early stages, immunotherapies may determine an inflammatory halo surrounding the tumor lesion reflecting the activation of the immune system and potentially mistaken for an increase in the overall size of the tumor [11]. Indeed, in patients with late responses to immunotherapy, assessment of therapy response based on RECIST may be erroneously considered positive, such as in a disease progression setting [12].

New immunotherapy drugs have changed imaging data as these new drugs have novel mechanisms of action and cause T-cell and immune activation, producing unusual response patterns resembling tumor growth to consider [13].

Therefore, a modified version of the WHO response criteria, the Immune-Related Response Criteria (irRC), was proposed in 2009 and then revised in 2013, promoting the use of one-dimensional measurements based on the RECIST original. Some recommendations were later published (referred to as irRECIST), but with poor reproducibility [13].

These criteria define different categories of response to therapy as unconfirmed progression (iUPD), progression confirmed (iCPD), complete response (iCR), partial response (iPR), and stable disease (iSD).

However, these criteria have several limitations as the inability to detect tumor heterogeneity and genetic profiles [14,15] and the limited ability in predicting programmed cell death or unusual responses like pseudo-progression or dissociated response [16–18].

Hence, the study of circulating biomarkers and imaging tools are the most promising ways currently proposed to overcome these limitations [19].

1.3. Radiomics and delta-radiomics

The role of medical imaging is rapidly evolving and becoming increasingly central in personalized precision medicine setting. Medical images contain numerous data not perceptible to the naked human eye, which may empower the diagnostic and prognostic evaluation of the patients far beyond the qualitative assessment [20,21].

Radiomics is based on the extraction from medical images of high-dimensional quantitative features, which has been widely used to develop predictive models [22,23].

Radiomic features may provide information about cancer's phenotype and indirectly also about cancer's genotype, as well as on the tumoral microenvironment [24–26].

Radiomic analysis could be used to correlate biological data with radiological images, possibly avoiding invasive procedures [27–30]. Furthermore, radiomics could also be useful in choosing the most suitable therapeutic in settings where multiple therapeutic options are available [31].

Radiomics has consequently aroused much interest in the scientific landscape and has been also studied as an imaging biomarker able to predict response to various immunotherapies.

Still, several limitations hinder the spread of radiomics, such as the lack of reproducibility and robustness [31,32]. Radiomics was commonly used to predict definite biological or clinical responses to treatment, but its potential role as a longitudinal biomarker of cancer response has yet to be fully explored [18,33,34].

Therefore, several studies have proposed a different method of analyzing image data, emphasizing the variations of radiomic features at different time points. This approach is a branch of radiomics defined as delta-radiomics [35].

Delta-radiomics has been proposed to predict the comparison of different timeline CT scans, by accessing changes in radiomic features over time [36] and, consequently, allowing assessment of changes that occurred during treatment after time or the introduction of external factors (e.g., chemotherapy or radiotherapy) [19].

At the same time, delta-radiomics is inherently more reproducible between different centres, with constant acquisition parameters [31].

This systematic review aims to investigate the role of delta-radiomics in the prediction of response to immunotherapy and to assess the current methodological quality of the radiomics-workflow.

2. Materials and methods

2.1. Literature search

A systematic literature review was performed to identify all relevant studies addressing the potential role of delta radiomics in predicting response to immunotherapy.

The examined electronic databases were Web Of Science, Scopus and PubMed. The search terms used to identify articles of potential interest were: "delta-radiomics AND immunotherapy". The selection of these terms was made to include all the articles addressing the potential role of delta-radiomics in immunotherapy response prediction.

The results were exported to Rayyan, which is a cloud-based platform for screening citation data [37].

After an automated duplicate elimination, all the articles were initially screened by reviewing their titles and abstracts. Two authors (C. B. and R.F.) independently selected the titles of the identified articles. Two other authors (E.A. and S.C.F.) independently screened the titles and abstracts of studies that passed the title screening. The full texts of the titles of the articles that passed the selection of titles and abstracts were retrieved. The discussion served to overcome any disagreements in the selection process, allowing for mutual agreement to be reached. The filters applied in the search process have allowed the selection of only original articles published in English, before 06/04/2023. No restrictions relating to the country of publication, study design or results were applied. The last search was done on 06/04/2023.

The following characteristics were collected for the included articles: year of publications, study design, number of patients, clinical setting, imaging technique, journal type (radiological journal or other), features

Table 1
Radiomics Quality Score items.

Criteria	Points
1. Image protocol quality	+ 1 (if protocols are well-documented) + 1 (if public protocol is used)
2. Multiple segmentations – possible actions are: segmentation by different physicians/algorithms/software, perturbing segmentations by (random) noise, segmentation at different breathing cycles. Analyze feature robustness to segmentation variabilities.	+ 1
3. Phantom study on all scanners – detect inter-scanner differences and vendor-dependent features. Analyze feature robustness to these sources of variability.	+ 1
4. Imaging at multiple time points – collect individuals' images at additional time points. Analyze feature robustness to temporal variabilities (e.g., organ movement, organ expansion/shrinkage).	+ 1
5. Feature reduction or adjustment for multiple testing – decreases the risk of overfitting. Overfitting is inevitable if the number of features exceeds the number of samples. Consider feature robustness when selecting features.	− 3 (if neither measure is implemented) + 3 (if either measure is implemented)
6. Multivariable analysis with non-radiomic features – is expected to provide a more holistic model. Permits correlating/inferencing between radiomics and non-radiomics features.	+ 1
7. Detect and discuss biological correlates – demonstration of phenotypic differences (possibly associated with underlying gene–protein expression patterns) deepens understanding of radiomics and biology.	+ 1
8. Cut-off analyses – determine risk groups by either the median, a previously published cut-off or report a continuous risk variable. Reduces the risk of reporting overly optimistic results.	+ 1
9. Discrimination statistics – report discrimination statistics (e.g., C-statistic, ROC curve, AUC) and their statistical significance (e.g., p-values, confidence intervals). One can also apply a resampling method (e.g., bootstrapping, cross-validation).	+ 1 (if discrimination statistic and its statistical significance are reported) + 1 (if a resampling method technique is also applied)
10. Calibration statistics – report calibration statistics (e.g., Calibration-in-the-large/slope, calibration plots) and their statistical significance (e.g., p-values, confidence intervals). One can also apply resampling method (e.g., bootstrapping, cross-validation).	+ 1 (if calibration statistic and its statistical significance are reported) + 1 (if a resampling method technique is also applied)
11. Prospective study registered in a trial database – provides the highest level of evidence supporting the clinical validity and usefulness of the radiomics biomarker.	+ 7 (for prospective validation on a radiomics signature in an appropriate trial)
12. Validation – the validation is performed without retraining and without adaptation of the cut-off value, provides crucial information with regard to credible clinical performance.	− 5 (if validation is missing) + 2 (validation with same) + 3 (with another institute) + 4 (with 2 datasets from two distinct institutes) + 4 (validates a published signature) + 5 (validation with dataset from ≥3 institutes)
13. Comparison to 'gold standard' – assess the extent to which the model agrees with/is superior to the current 'gold standard' method (e.g., TNM-staging for survival prediction). This comparison shows the added value of radiomics.	+ 2
14. Potential clinical utility – report on the current and potential application of the model in a clinical setting (e.g., decision curve analysis).	+ 2
15. Cost-effectiveness analysis – report on the cost-effectiveness of the clinical application (e.g., quality adjusted life years generated).	+ 1
16. Open science and data – make code and data publicly available. Open science facilitates knowledge transfer and reproducibility of the study.	+ 1 (open-source scans) + 1 (open-source ROI) + 1 (open-source code) + 1 (open-source calculated features) Total points (36 = 100 %)

Abbreviations: AUC: area under the curve.

type (first-order or more), radiomics-features analysis type (machine learning or others).

2.2. Radiomics Quality Score

The Radiomic Quality Score (RQS) according to Lambin et al. [38] was used to assess the methodological quality of the included articles. RQS is an assessment tool made up of 16 items, with different maximum scores according to their importance. The summed scores of all 16 items range from − 8 to 36. To calculate percentages, a score of 0 % was assigned to studies with summed scores from − 8 to 0, while a score of 100 % was assigned to studies with a summed score of 36. Two reviewers (C.B. and M.F.) independently rated the included papers. Disagreements between the two reviewers were resolved in consensus together with a third reviewer (S.C.F). RQS criteria and scores are shown in the Table 1.

3. Results

The flowchart of all the harvested papers is shown in Fig. 1.

A total of 23 duplicates and 4 unrelated papers were removed. Overall, 13 articles were finally included in the review. The first included study to be issued was published in 2019, two studies in 2020, three in 2021, four in 2022, and finally three in 2023. All the articles were published in non-radiological journals and were retrospective studies. The mean patient number was 92,07 ± 61,28. The most frequently addressed clinical setting was the prediction of response to immunotherapy of non-small-cell lung cancer (NSCLC) (6/13, 46 %), followed by metastatic melanoma (3/13, 23 %). In the vast majority of papers, CT was used as the imaging technique (11/13, 84 %), while MRI and FDG-PET/CT were used in only one study each. Slightly under half of the included articles (6/13, 46 %) employed machine learning techniques for model building. Characteristics of the included articles are resumed in Table 2.

Overall, the RQS of the included studies ranged from 4 to 17, with a mean RQS total of 11,15 ± 4,18 with a corresponding percentage of 30.98 ± 11.61 %. The detailed RQS assessment for each of the included articles is reported in Table 3.

As expected according to the scope of the review, most of the articles (11/13, 84.61%) performed imaging at multiple time-points, except in two studies where delta radiomics features were calculated between different acquisition phases and not between different exams. The same proportion of studies clearly reported the imaging protocol. Notably, all the included articles carried out feature reduction or adjustment for multiple testing, to reduce the risk of overfitting, and discussed the relationship between the delta radiomics-based signature and biology.

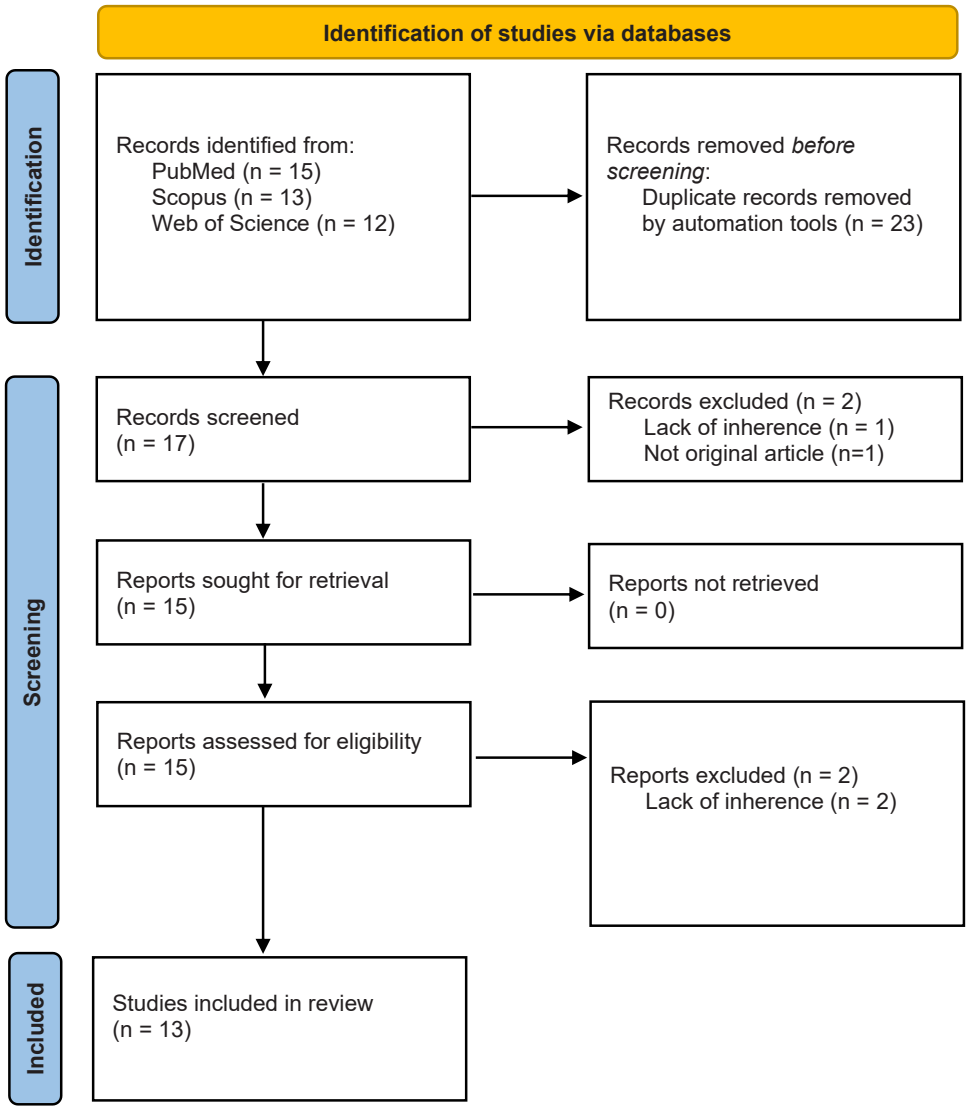

Fig. 1. Study selection process flowchart according to the PRISMA Statement 2020 [39].

Table 2
Characteristics of the included articles.

First author	Publication year	Study design	Number of patients	Clinical setting	Imaging technique	Journal (Radiological or not radiological)	Features (First order/more)	ML (Yes/No)
Gong [40]	2022	Retrospective	224	NSCLC[a]	CT	Not Radiological	More	Yes
Rundo [41]	2019	Retrospective	43	Bladder Cancer	CT	Not Radiological	More	Yes
Ho [42]	2023	Retrospective	26	HCC[a]	MRI	Not Radiological	More	No
Khorrami [43]	2020	Retrospective	139	NSCLC	CT	Not Radiological	More	No
Xie [44]	2022	Retrospective	97	NSCLC	CT	Not Radiological	More	No
Qu [45]	2023	Retrospective	76	Colorectal liver metastases	CT	Not Radiological	More	Yes
Liu [46]	2021	Retrospective	197	NSCLC	CT	Not Radiological	More	No
Guerrisi [47]	2021	Retrospective	78	Metastatic Melanoma	CT	Not Radiological	More	No
Barabino [19]	2022	Retrospective	33	NSCLC	CT	Not Radiological	More	No
Chen [48]	2021	Retrospective	50	Metastatic Melanoma	CT	Not Radiological	More	Yes
Li [49]	2023	Retrospective	101	Gastric Cancer	CT	Not Radiological	More	No
Wang [50]	2020	Retrospective	50	Metastatic Melanoma	CT	Not Radiological	More	Yes
Tankyevych [51]	2022	Retrospective	83	NSCLC	FDG-PET/CT	Not Radiological	More	Yes

[a] NSCLC Non-small-cell lung cancer, HCC Hepatocellular carcinoma.

Table 3
Radiomics quality scores of the included articles.

First author	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	RQS (Total)	RQS (%)
Gong [40]	1	0	0	1	3	0	1	0	2	0	0	4	2	2	0	0	16	44,44
Rundo [41]	0	0	0	1	3	1	1	0	1	0	0	2	2	0	0	0	11	30,56
Ho [42]	1	0	0	0	3	0	1	0	1	0	0	-5	2	0	0	0	4	11,11
Khorrami [43]	1	0	0		3	0	1	0	2	0	0	2	2	0	0	0	12	33,33
Xie [44]	1	1	0	1	3	1	1	1	1	1	0	2	2	2	0	0	17	47,22
Qu [45]	1	1	0	0	3	1	1	0	1	1	0	2	2	0	0	0	13	36,11
Liu [46]	1	1	0	1	3	1	1	0	1	1	0	2	2	2	0	0	16	44,44
Guerrisi [47]	1	1	0	1	3	1	1	1	2	0	0	-5	2	2	0	0	10	27,78
Barabino [19]	1	0	0	1	3	0	1	0	1	0	0	-5	2	0	0	0	4	11,11
Chen [48]	1	0	0	1	3	0	1	0	1	0	0	2	2	0	0	0	11	30,56
Li [49]	1	1	0	1	3	1	1	1	1	0	0	-5	2	0	0	0	7	19,44
Wang [50]	1	1	0	1	3	0	1	0	2	0	0	2	2	0	0	0	13	36,11
Tankyevych [51]	1	0	0	1	3	0	1	0	1	0	0	2	2	0	0	0	11	30,56

*RQS Radiomics Quality Score.

The delta radiomics-based models have been validated in 9 articles out of 13 (69%), but in only one study (7 %) the validation was based on external datasets.

No study carried out phantom studies, prospective validation, decision curve analysis, cost-effectiveness analysis or used publicly available code and data.

4. Discussion

With the advent of immunological therapies, the diagnostic, therapeutic and clinical scenario in the oncological field has moved a step forward towards personalized medicine. The evaluation of responses to therapies, such as the phenotype and genotype of the tumor has become fundamental. However, the effectiveness of the rapidly evolving therapeutic landscape in immuno-oncology largely depends on the development of imaging biomarkers for treatment response evaluation [52,53]. The possibility of extracting data not visible to the human eye from medical images and their consequent analysis has opened new diagnostic and consequently therapeutic possibilities. Radiomics has shown promising results both in guiding the best therapeutic path for the patient, in the early diagnosis of cancer, and in providing reliable prognostic data [54].

In this scenario, delta radiomics has become a priority for researchers, as highlighted by some of the results of the papers included in this systematic review. Delta-radiomics signatures were demonstrated able to effectively differentiate responders from non-responders in patients with advanced NSCLC, metastatic bladder cancer and metastatic melanoma undergoing immunotherapy [40,55–58]. Similarly, Li et al. showed that DVintra_original_glszm_Zone Variance was an independent predictor for free-progression-survival in patients with advanced gastric cancer treated with ICIs [59]. This evidence was also observed with more complex treatment strategy, as in the study by Ho et al. where delta radiomics was able to predict response in patients with hepatocellular carcinoma undergoing sequential trans-arterial chemoembolization plus stereotactic body radiotherapy plus immunotherapy [60].

Delta radiomics may also represent a solution when conventional radiomics fails. Liu et al. failed to predict response to anti-PD-1 immunotherapy in patients with advanced NSCLC using conventional radiomics, while they were successful using a delta radiomics signature [61].

Similarly, Qu et al. demonstrated that dynamic radiomics features, i.e. delta radiomics features calculated between different acquisition phases, better predicted the efficacy of immunotherapy in patients with colorectal liver metastases compared to conventional radiomics [62]. An additional benefit may derive from the combination of the two approaches, as shown by Chen et al. [63] who obtained more reliable results in the prediction of treatment response in patients with metastatic melanoma when merging conventional and delta radiomics.

Similarly, delta radiomics may be combined with clinical and pathological patterns to develop predictive nomograms, which could lead toward precision treatment plans [44].

Delta radiomics may be also helpful in differentiating pseudoprogression (pPD) from progressive disease (PD). Barabino et al. [19] found that the variation of 27 features was predictive of the radiologic response of NSCLC patients to ICIs. A secondary relevant result of this study was that the delta-radiomics signature distinguishing pPD from PD differed from those distinguishing responders from non-responders.

A better understanding of the correlation between delta radiomics signature and radiological response requires the investigation of the biological correlates of these features. Khorrami et al. [34] hypothesized that the increase of Gabor features [64] was associated with a higher number of inflammatory cells in the tumoral and peritumoral compartment [65], while the increase of Haralick features with hypoxia and acidosis [66], which are known to have an inhibitory effect on T cells and to weaken immunotherapy efficacy [67–70]. Variations in Laws and CoLlage features were correlated with peritumoral vascular

invasion, neovascularization, and changes in structural orientation [71, 72].

The methodological quality of the articles included in this systematic review was assessed using the RQS [38]. The mean RQS percentage was 30.98, which is far from ideal, but still slightly higher compared to the median of 21.00 calculated across all the systematic reviews using RQS calculated by the EuSoMII Radiomics Auditing Group [73]. The divergence narrows if, in the same review, we consider only the subgroup of systematic reviews addressing radiomics application in oncologic imaging, which reached a median of 27.3 [73].

Despite the limited number of reviewers, which is a limitation of this study, the use of RQS allowed us to highlight some methodological issues in common among the included papers. First, the complete shortage of prospective studies and cost-effectiveness analysis, which sums up the current distance between delta radiomics and clinical practice. Second, the lack of external validation, which is pivotal to confirming the generalizability of the delta radiomics-based models. Third, no study made data and code publicly available, thus restraining the repeatability of these studies. However, also some strengths have emerged. In all the included papers the relationship between the delta radiomics signature and biological correlates was discussed, as well as a feature reduction technique was always reported.

This means that a certain degree of standardization is finally being achieved in the scientific community in radiomics research methodology, and hopefully, this will become increasingly true with the introduction of a checklist addressing this topic [32,74].

In conclusion, the applications of delta radiomics in the assessment of treatment response are promising, but further studies with prospective design and large-scale multicentric cohorts are needed to confirm these results. Unusual outcomes of immunotherapy as pPD are currently underinvestigated, and further research is required. The use of immunotherapy drugs now involves many other types of cancers, and the role of delta radiomics must be confirmed in these clinical settings as well.

CRediT authorship contribution statement

Maria Febi: Visualization, Methodology, Formal analysis, Data curation. **Gayane Aghakhanyan:** Writing – review & editing, Visualization, Supervision. **Claudio Bandini:** Writing – original draft, Methodology, Data curation. **Roberto Francischello:** Writing – original draft, Visualization, Data curation. **Riccardo Antonio Lencioni:** Writing – review & editing, Visualization, Supervision. **Dania Cioni:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization. **Ilaria Ambrosini:** Writing – review & editing, Writing – original draft, Visualization, Supervision. **Lorenzo Faggioni:** Writing – review & editing, Visualization, Supervision, Conceptualization. **Engy Abbas:** Methodology, Data curation. **Salvatore Claudio Fanni:** Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Emanuele Neri:** Writing – review & editing, Visualization, Supervision, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Lorenzo Faggioni is an Editorial Board Member of European Journal of Radiology Open. Given his role as Editorial Board Member, had no involvement in the peer-review of this article and has no access to information regarding its peer-review.

Acknowledgements

The research leading to these results has received funding from the European Union - NextGenerationEU through the Italian Ministry of University and Research under PNRR - M4C2-I1.3 Project PE_00000019 "HEAL ITALIA" to Salvatore Claudio Fanni, Riccardo Antonio Lencioni and Emanuele Neri, CUP of University of Pisa. The views and opinions expressed are those of the authors only and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them

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