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SPECIAL SECTION: OVARIAN CANCER

Radiomics and radiogenomics in ovarian cancer: a literature review

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Abstract

Ovarian cancer remains one of the most lethal gynecological cancers in the world despite extensive progress in the areas of chemotherapy and surgery. Many studies have postulated that this is because of the profound heterogeneity that underpins response to therapy and prognosis. Standard imaging evaluation using CT or MRI does not take into account this tumoral heterogeneity especially in advanced stages with peritoneal carcinomatosis. As such, newly emergent fields in the assessment of tumor heterogeneity have been proposed using radiomics to evaluate the whole tumor burden heterogeneity as opposed to single biopsy sampling. This review provides an overview of radiomics, radiogenomics, and proteomics and examines the use of these newly emergent fields in assessing tumor heterogeneity and its implications in ovarian cancer.

Keywords Ovarian cancer · Radiomics · Proteomics · Radiogenomics

Introduction

Ovarian cancer remains one of the most lethal gynecological cancers in the world with the epithelial subtype accounting for more than 90% of all cases and being responsible for the vast majority of ovarian cancer-related deaths [1]. Although progress has been made through refinements in chemotherapeutic and surgical approaches, patient survival and prognosis have only improved slightly in the recent years [2–7]. Many studies have postulated that this is because the disease cannot be defined as a single entity, but rather consists of a vast degree of cellular and genomic heterogeneity that dictate response to therapy and prognosis [8–15]. This heterogeneity can be divided into inter- and intra-tumoral heterogeneity [15, 16]. Inter-tumoral heterogeneity is defined as the genotypic and phenotypic variations found between multiple tumor implants in the peritoneal cavity while intra-tumoral heterogeneity is recognized as the coexistence of different cell populations within one single lesion [16]. Two models used to explain this inter- and intra-tumoral heterogeneity have been proposed based on deep spatial and longitudinal DNA sequencing studies of ovarian tumors and matched peritoneal implants [17–19]. In linear evolution, distinct populations of cells arise in the primary ovarian tumor, from which cells then break off to form secondary sites. In parallel evolution, both primary ovarian tumors and metastases continue to evolve, with new populations of metastases arising and even reseeding the primary site of metastases (Fig. 1) [18].

Next-generation sequencing has documented the genome of primary ovarian cancer, identifying potential therapeutic targets [20–23]. Far less analysis has been performed on peritoneal implants due to the difficulty in accessing metastatic tissues, therefore a number of important clinical and biological queries remain unanswered. The large number of peritoneal implants, their accessibility, and their imaging presentation mean that analyzing high-grade serous ovarian carcinoma (HGSOC) by single biopsy sampling and traditional imaging tools is extremely challenging. Computed

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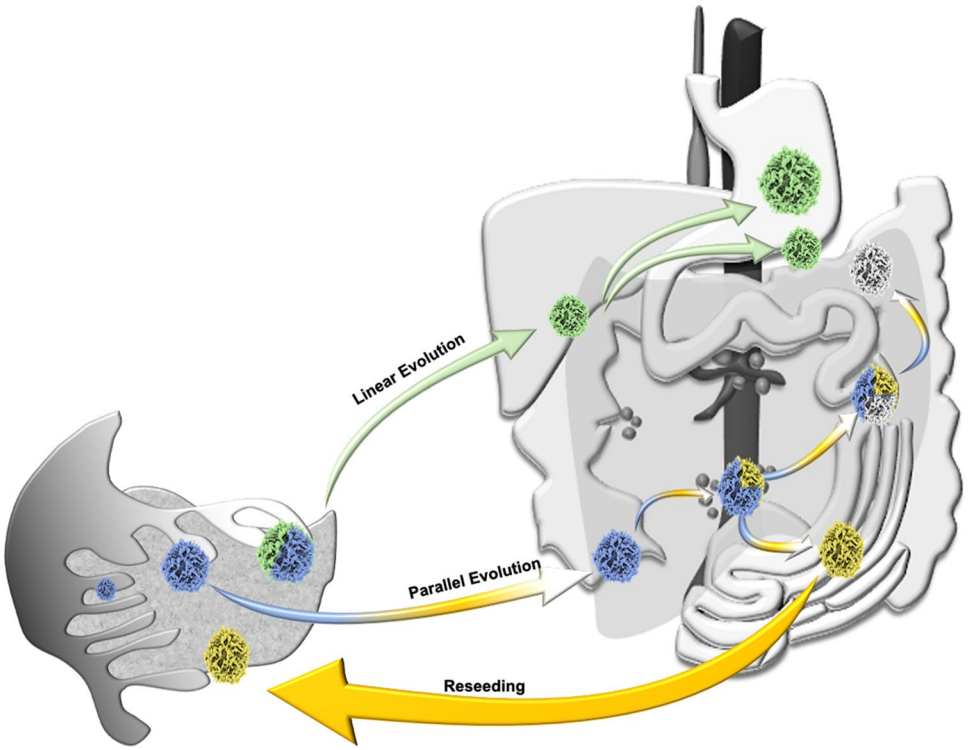

Fig. 1 Drawing demonstrating the linear and parallel model explaining tumor heterogeneity: In the linear progression model, metastasis is seeded at a late stage of tumor progression, resulting in minimal genetic divergence between the primary tumor and its metastases. In the parallel progression model, metastases are seeded early in tumor progression, so high levels of genetic divergence are expected between the primary tumor and its metastases, even reseeding the primary tumor

tomography (CT) and, in selected cases magnetic resonance imaging (MRI), have been used to evaluate the extent of disease and monitor treatment response in patients with HGSOC providing mainly an understaging of the disease burden [24–31]. Tools to capture the heterogeneity of the disease at an imaging level are emerging [32–34]. Imaging research is particularly focused on the field of radiomics [33, 35–39]. Radiomics is defined as the extraction of a large level of quantitative data from images which cannot be assessed visually [32, 34]. The quantification of heterogeneity on imaging in ovarian cancer may offer an opportunity to noninvasively evaluate the whole tumor volume, i.e., ovarian tumor and peritoneal implants rather than single biopsy evaluation. This would allow better prediction of outcome, optimal triage, and the ability to offer the best treatment option for every patient [36].

This review provides an overview of radiomics, radiogenomics, and proteomics, and examines the use of these newly emergent fields in assessing tumor heterogeneity and its implications in ovarian cancer.

Ovarian cancer: where are we now in terms of imaging?

Tremendous advances in risk stratification have been made by establishing standardized and evidence-based risk assessment algorithms using both ultrasound and MRI, allowing accurate characterization of the adnexal lesions [40, 41].

For ultrasound, the International Ovarian Tumor Analysis (IOTA) group has developed the simple rules classification system and Assessment of Different Neoplasia in the Adnexa (ADNEX) model to differentiate benign from malignant adnexal masses [42–47]. Other ovarian mass characterization and management systems have been proposed, including the Society of Radiologists in Ultrasound consensus statement [48, 49] and the Gynecologic Imaging Reporting and Data System, or GI-RADS [40, 50].

Most recently, the Ovarian-Adnexal Reporting and Data System (O-RADS) published in 2018 has provided a standardized lexicon that includes all pertinent descriptors and definitions of the characteristic ultrasound appearance of normal ovaries and ovarian lesions [40]. Based on this validated reporting system, ultrasound guidelines for lesion management have been proposed in 2020 [51]. These guidelines now include all risk categories with their corresponding management strategies, which had not been presented in any of the previous versions [51].

However, approximately 18% to 31% of adnexal lesions detected on ultrasound remain indeterminate, with MRI recognized as the complementary tool to assess indeterminate ovarian lesion on ultrasound [52]. The European Society of Urogenital Radiology (ESUR) recommendation has proposed an algorithmic approach to help differentiate benign from malignant lesions [53]. More recently an O-RADS MRI, similar to O-RADS ultrasound, has been proposed. This 5-category MRI scoring system was initially developed in a retrospective single-center study [41] using

indeterminate adnexal masses on ultrasonography and was subsequently validated prospectively on 1340 women. Area under the receiver operating characteristic curve for differentiating benign from malignant lesions was 0.961 (95% CI 0.948–0.971) among experienced readers, with a sensitivity of 0.93 (95% CI 0.89–0.96; 189 of 203 patients) and a specificity of 0.91 (95% CI 0.89–0.93; 848 of 927 patients) [54].

For peritoneal implants, less advances have been made. CT remains the imaging gold standard for preoperative evaluation, with an accuracy ranging between 70 and 90% for implant detection [29, 55–58]. CT, however, has a limited sensitivity (25% to 50%) for implants less than 1 cm, particularly in locations such as the bowel surface or mesentery [55]. Implant detection is improved by the opacification of the gastrointestinal tract which helps to differentiate bowel from serosal and mesenteric implants. Reformatted images in coronal and sagittal planes are particularly useful for evaluating the subphrenic space [57].

The role of MRI in peritoneal disease staging has recently been evaluated. Promising results and guidelines have been proposed at the 10th Peritoneal Surface Oncology Group International (PSOGI) congress 2016. For now, MRI serves mainly as an adjunct to CT for implant detection. Standard MRI has the same sensitivity as CT in the detection of peritoneal deposits [29, 59]. However, the use of fat suppression, delayed post-contrast imaging, oral contrast agents, and functional imaging such as DWI [60] have allowed the detection sensitivities of MRI to surpass CT [61, 62] with sensitivity and specificity of DWI being 90% and 95.5%, respectively, for implant detection [60].

Response evaluation to chemotherapy by imaging also remains challenging. CT does not provide a quantitative assessment of disease response to cytotoxic therapy and does not reflect molecular events in the tumor (apoptosis, necrosis etc.) as it relies solely on macroscopic changes in tumor size as per Response evaluation criteria in solid tumors (RECIST) criteria [63]. The use of RECIST is often not possible as the carcinomatosis frequently consists of multiple subcentimeter nodules, ill-defined soft tissue masses, confluent disease or disease of a diffuse infiltrative pattern not eligible for RECIST evaluation. Functional imaging using diffusion-weighted imaging (DWI) has been evaluated in the research setting. Using ADC histograms, authors have shown efficacy in treatment monitoring of peritoneal carcinomatosis [64].

However, all evaluation of peritoneal disease by either CT or multiparametric MRI requires the subjective interpretation of a radiologist to inform the clinician on the volume and location of the many implants. This approach inevitably introduces a high degree of variability. Tools for more automated imaging analyses have been tested, not only to reduce this variability, but to provide more objective, clinically relevant information [65]. Following the steps of genomics, in the era of big data, a new field in medical imaging has emerged under the label of ''radiomics.'' Radiomics has been introduced as an emergent tool for postprocessing CT or MR images and developing new quantification metrics [66–72] linking qualitative and/or qualitative imaging data to clinical endpoints. Compared to Computer Aided Detection (CAD) in which the number of image features involved is usually less than 20, radiomics deals with hundreds to thousands of imaging features extracted from large-scale radiological images. These quantitative metrics have been shown to provide important insights into tumor biology, linking quantitative imaging data to meaningful clinical endpoints. Of particular interest is the potential ability of image-derived metrics to reliably identify important tumor subregions noninvasively and derive predictive imaging biomarkers.

Radiomics: how does it work? (Fig. 2)

The process of radiomics analysis encompasses the following steps:1/image acquisition and segmentation, 2/feature extraction, 3/feature selection, and 4/ model construction [73, 74].

(1) *Image acquisition* represents the first step. Radiomics analysis can be applied to any type of medical images, including X-ray, US, CT, MRI, and PET-CT. Before radiomic features are calculated, a region of interest or volume of interest encompassing the dedicated area has to be defined. Currently, there are a number of reliable algorithms capable of automatic or semi-automatic lesion segmentation, limiting the need for human input, helping overcome subjectivity and time cost associated with manual segmentation [75, 76]. However, in some instances, performance of these algorithms is jeopardized by the complexity of the task mainly due to the complex appearance of the lesion (ill-defined borders, locations adjacent and not being easily distinguishable from adjacent anatomical structures). Under these circumstances, expert manual segmentation and delineation of the ROI on one chosen slice (2D) or on the entire volume (3D) remain the only valid option [77–80].

(2) *Feature extraction*, requiring the use of dedicated software or open-source programming packages, offers many options, from pre-processing tools including normalization, resampling, and discretization, to customizing the extraction and enabling the application of additional filters on the original images [81–83].

The process of extraction returns a large amount of quantitative imaging metrics, which can be categorized in 6 different groups: a/First-Order Statistics are

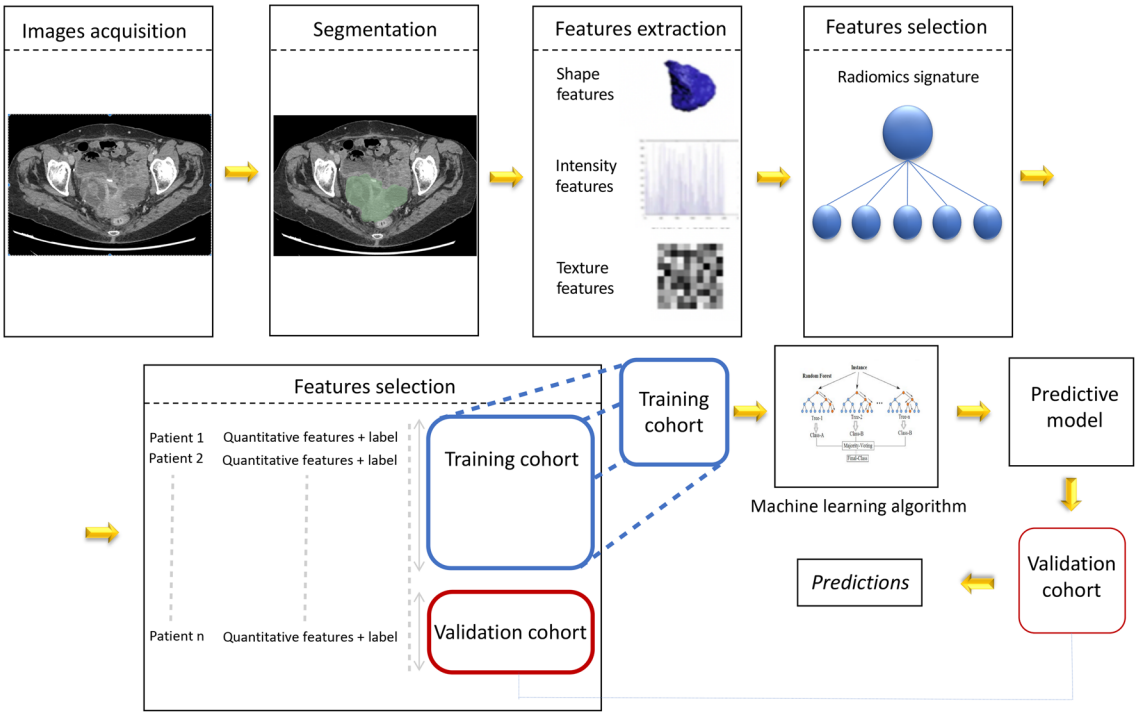

Fig. 2 Schematic summarizing the process of radiomics

features related to the histogram, including energy, entropy, kurtosis, skewness … b/Shape-based features, such as volume, surface area, sphericity… The following groups include textural features, and assess the spatial distribution of pixel intensities: c/Gray-Level Co-occurence Matrix, d/Gray-Level Run Length Matrix, e/Gray-Level Size Zone Matrix, and f/Gray-Level Dependence Matrix.

A large number of features (between 50 and 5000) are usually extracted. These are then decreased through feature qualification in order to select only the features that are informative and reproducible and to prevent the risk of overfitting [84]. Overfitting is defined as the construction of an analytical process that corresponds too closely to a specific dataset, with the model performing poorly in the validation phase in contrast to its learning phase, and consequently failing to generalize.

(3) *Feature selection* The process of feature selection usually starts with removing redundant features [85]. Secondly, inter-observer and intra-observer feature variability are assessed. Highly variable features are not considered in model construction as they may yield too hazardous results [86]. Thirdly, only important features with high correlation to the studied endpoint are selected. The number of optimal selected features might vary depending on the dataset, but no consensus on the exact number has been achieved. Yet, Parmar et al. suggest that number should be equal to the square root of the number of observations in a correlated set of features. Selected features constitute what we—in the literature—refer to as the ''Radiomics signature' [87]'.

(4) *Model construction and performance assessment* The goal is to develop a mathematical or a statistical model to be associated with a diagnosis, tumor response, or patient outcome. In other words, the model is equivalent to an algorithm that analyzes training data and infers a hypothesis to predict a variable when given quantitative imaging features. Different algorithms have been proposed. The most popular include the following: random forest (RF) [88], least absolute shrinkage and selection operator (LASSO) [89], artificial neural networks (ANN) [90], support vector machine (SVM) [91], and minimum redundancy maximum relevance (mRMR) [92]. No consensus on the pre-eminent algorithm has been achieved, as one algorithm might outperform another depending on the dataset type and variables [93]. To quantify the discrimination performance, the AUC or the Harrell concordance index is used. Validation of the model could be assessed either internally or externally. In internal validation, the most common procedure is the ''leave-one out'' cross-validation (LOOCV) where all the data are used for training except for one data point, which is left out for testing and validation [94]. Another common method

is the bootstrap, which consists of generating a large series of data (bootstrap sample) [95]. Each bootstrap sample represents a patient chosen randomly, combined with its corresponding features and outcome, and this process is reiterated over the entire cohort of patients.

Radiomics and radiogenomics in ovarian cancer (Fig. 3) (Table 1)

Work on radiomics and radiogenomics has been mainly linked with genomic advances thanks to The Cancer Genome Atlas (TCGA) research network [96, 97]. Based on the TCGA data, a prognostic algorithm for HGSOC known as Classification of Ovarian Cancer (CLOVAR) has been defined with four subtypes: differentiated, immunoreactive, mesenchymal, and proliferative [98, 99]. Patients with mesenchymal subtype have been shown to have a higher rate of platinum resistance (63%) compared with patients with other subtypes (23%), as well as shorter median survival (23 vs 46 months for patients). Initially, Vargas et al. explored the relationships between subjective qualitative CT features and CLOVAR subtypes of HGSOC [100]. The authors found that CLOVAR mesenchymal subtype was significantly associated with higher risk of peritoneal involvement and the presence of mesenteric infiltration on CT. These results may explain the reported poorer prognosis of patients with the CLOVAR mesenchymal subtype of HGSOC [99]. However, in a subsequent study, the same research team showed the limit of subjective qualitative assessment of CT with poor inter-observer agreement in the assessment of this feature (mesenteric infiltration) ($\alpha = 0.23$) when reviewed by eight readers. As such, the limitations of subjective evaluation support the use of for more automated or semiautomated analysis [101].

In another study including 38 patients, Vargas et al. developed 12 quantitative metrics to capture spatial inter-site imaging heterogeneity in high-grade serous ovarian cancer [102]. The authors demonstrated that metrics capturing the differences in texture similarities across sites were associated with shorter overall survival (inter-site similarity entropy, similarity-level cluster shade, and inter-site similarity-level cluster prominence; $p \leq 0.05$) and incomplete surgical resection (similarity -level cluster shade, inter-site similarity-level cluster prominence, and inter-site cluster variance) [102].

Rizzo et al. evaluated whether CT radiomics features extracted from the primary tumor alone or combined with clinical data were associated with residual tumor at surgery in 101 patients with ovarian cancer and were able to predict the risk of disease progression within 12 months [33]. The authors found that features related to mass size, randomness and homogeneity were associated with residual tumor at surgery. At multivariate analysis, the risk of progression at 12 months was associated with one feature, F2 shape/Max3DDiameter, related to tumor size [33]. Adding this radiomic feature to a clinically based model significantly increased prediction of progression at 12 months by 14%

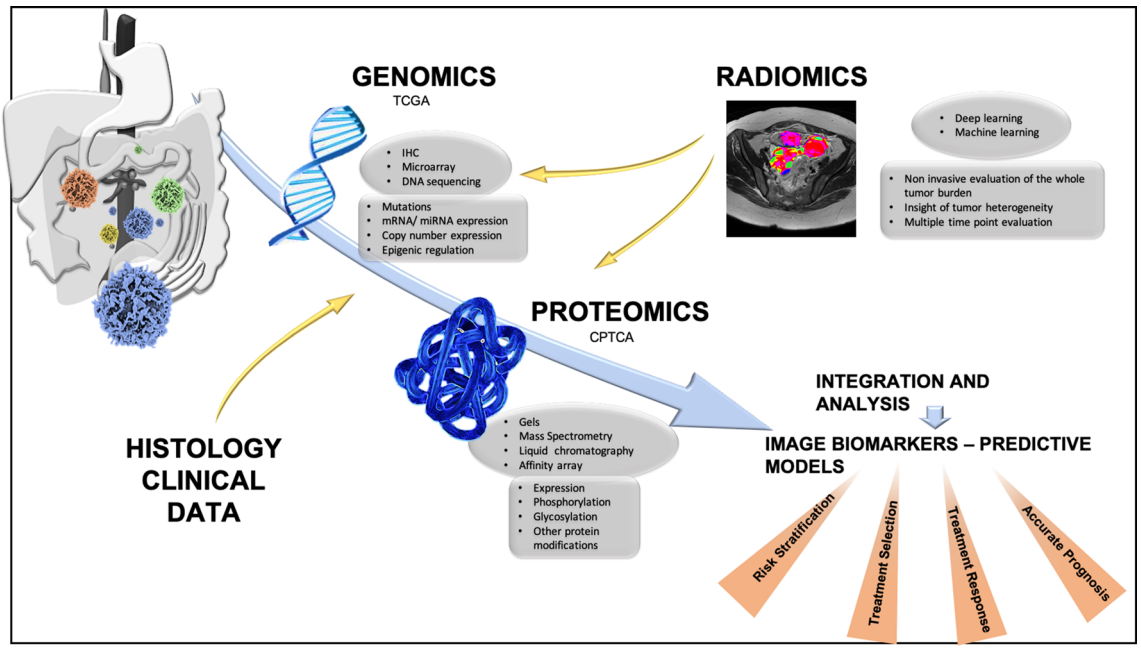

Fig. 3 Schematic summarizing the integration of radiomics to clinical data, genomics, and proteomics to build highly powerful predictive models

Table 1 Summary of literature on radiomics in ovarian cancer

Author	Year	*N*	Lesion	CT/MRI	Aim	Result
Vargas et al.	2017	38	Primary tumor + peritoneal disease	CT	Association between CT radiomics features to capture spatial inter-site imaging heterogeneity, residual tumor at surgery and survival	Features capturing the differences in texture similarities across sites were associated with shorter overall survival and incomplete surgical resection
Rizzo et al.	2019	101	Primary tumor	CT	Association between CT radiomics features alone or combined with clinical data, residual tumor at surgery and risk of disease progression within 12 months	Features related to mass size, randomness and homogeneity were associated with residual tumor at surgery Risk of progression was associated with one feature, F2 shape/Max3DDiameter (related to tumor size). Combining this radiomic feature with a clinical model significantly increased prediction of progression by 14%
Meier et al.	2019	88	Primary tumor + peritoneal disease	CT	Associations between inter-site texture heterogeneity parameters derived from CT, survival, and BRCA mutation status	High inter-site cluster variance was associated with lower progression free survival (PFS) and overall survival (OS) Higher inter-site cluster prominence was associated with lower PFS and higher inter-site cluster entropy correlated with lower OS High values of all three features were significantly associated with lower complete surgical resection status in BRCA-negative patients None of the features were able to distinguish between BRCA mutation carrier and non-mutation carrier
Lu et al.	2019	364	Primary tumor	CT	Association between CT radiomics features, survival, genomic, transcriptomic and proteomic	Forty-two radiomic features were significantly associated with OS; these 42 radiomic features were further reduced to 4 weighted features. The weighted sum of these four radiomic features gave a "radiomic prognostic vector" score for each tumor that reliably identified the 5% of patients with median overall survival less than 2 years Radiomics was linked to genomic, transcriptomic and proteomic pattern. Poor survival was associated with stomal type tissue
Zhang et al.	2019	289	Primary tumor	MR	MR Radiomics model to discriminate benign from malignant ovarian tumors and to differentiate between type I and type II epithelial ovarian cancer	MR radiomics model showed higher accuracy than that of the radiologists (90.6% and 83.5%, respectively to differentiate between benign and malignant lesion) MR radiomics model showed an accuracy of 83% and an AUC of 85% to differentiate between type I and type II epithelial ovarian cancer
Qian et al.	2020	61	Primary tumor	MR	Comparison of the performance of clinical features, conventional MR image features, ADC value, T2WI, DWI, DCE MR radiomics, and a combined multiple features model to predict the type of epithelial ovarian cancer	Traditional model achieved the best diagnostic performance, while the diagnostic efficacy of the mixed model was slightly increased, thus concluding that the traditional model represents a non-invasive and reliable tool that can better distinguish epithelial ovarian cancer type I from epithelial ovarian cancer type II preoperatively

Table 1 (continued)

Author	Year	*N*	Lesion	CT/MRI	Aim	Result
Wang et al.	2020	31	Primary tumor		Development of a classification model to identify ex vivo benign, malignant and normal ovarian tissue	A classification between benign, malignant, and normal fresh ex vivo ovarian tissue was developed with performance values at AUC-ROC of 0.98, 0.96, and 0.94, respectively combining the minimum-redundancy maximum-relevancy feature selection method and a tree-based pipeline optimization tool
Beer et al.	2020	20	Primary tumor + peritoneal disease	CT	Association texture metrics with proteomic data	The abundance of three proteins was associated with texture features that represented intra-and inter-site tumor heterogeneity, with the strongest negative correlation between the CKB protein and cluster dissimilarity ($p = 0.047$, tau = 0.326)
Song et al.	2020	104	Primary tumor	MR	Evaluation of the efficiency of 2- and 3-class classification predictive tasks constructed from radiomics features extracted from DCE-MRI to discremine benign, borderline, and malignant ovarian tumors	The 2-class classification task was divided into three subtasks: benign vs. borderline (task A), benign vs. malignant (task B), and borderline vs. malignant (task C). For the 3-class classification task, 104 lesions were randomly divided into training (72 lesions) and validation (32 lesions) cohorts. For the 2-class classification task, the combination of radiomics signatures model showed a good diagnostic ability with the highest AUCs of 0.899, 0.865, and 0.893 for tasks A, B, and C, respectively. The 3-class classification task demonstrated a good discrimination performance with AUCs of 0.893, 0.944, and 0.891 for the benign, borderline, and malignant groups, respectively
Jian et al.	2020	294	Primary tumor	MR	MR image-based radiomics model to differentiate between type I and type II EOC	Quantitative MR imaging features were extracted from the following axial sequences: T2WI FS, DWI, ADC, and CE-T1WI. A combined model was constructed based on the combination of these four MR sequences. Combined radiomics model exhibited superior diagnostic capability over all four single-parametric radiomics models, both in internal and external validation cohorts (AUC of 0.806 and 0.847, respectively)

(AUC = 0.73 for clinical model vs 0.87 for clinical radiomic model) [33].

More recently, Meier et al. assessed the associations between inter-site texture heterogeneity parameters derived from CT, survival, and BRCA mutation status in women with high-grade serous ovarian cancer [103]. The authors demonstrated that high inter-site cluster variance was associated with lower progression-free survival (PFS) ($p = 0.006$) and overall survival (OS) ($p = 0.003$). Higher inter-site cluster prominence was associated with lower PFS ($p = 0.02$) and higher inter-site cluster entropy correlated with lower OS ($p = 0.01$). High values of all three metrics were significantly associated with lower complete surgical resection status in BRCA-negative patients (SE $p = 0.039$, SCV $p = 0.006$, SCP $p = 0.02$), but not in BRCA-positive patients (SE $p = 0.7$, SCV $p = 0.91$, SCP $p = 0.67$). However, none of the metrics were able to distinguish between BRCA mutation carrier and nonmutation carrier [103].

With the aim of developing a novel radiomics-determined mathematical descriptor of epithelial ovarian cancer tumor risk phenotype with a predictive value, Lu et al. extracted 657 quantitative mathematical descriptors from the preoperative CT scans of 364 ovarian cancer patients at their initial presentation [104]. The cohorts were divided into discovery dataset ($n = 136$), validation dataset ($n = 77$), and external dataset evaluated with the TCGA ($n = 70$). Forty-two radiomic features were significantly associated with OS; these 42 radiomic features were further reduced to 4 weighted features using least absolute shrinkage and selection operator method. The weighted sum of these four radiomic features gave a "radiomic prognostic vector" score for each tumor that reliably identified the 5% of patients with median overall survival of less than 2 years [104].

Textural features are gaining interest not only from CT studies, but also from MR studies and ex vivo studies. For example, Song et al. evaluated the efficiency of 2- and 3-class classification predictive tasks constructed from radiomics features extracted from Dynamic contrast enhancement (DCE)-MRI in discriminating among benign, borderline, and malignant ovarian tumors in 104 ovarian lesions [105]. The 2-class classification task was divided into three subtasks: benign vs. borderline (task A), benign vs. malignant (task B), and borderline vs. malignant (task C). For the 3-class classification task, 104 lesions were randomly divided into training (72 lesions) and validation (32 lesions) cohorts. For the 2-class classification task, the radiomics model showed a good diagnostic ability with the highest AUCs of 0.899, 0.865, and 0.893 for tasks A, B, and C, respectively. The 3-class classification task demonstrated a good discrimination performance with AUCs of 0.893, 0.944, and 0.891 for the benign, borderline, and malignant groups, respectively [105]. More recently, Zhang et al. evaluated again the diagnostic performance of a radiomics model based on MR images to discriminate benign ovarian tumors from malignancies using features from multiple sequences (T1, T2WI, T2WI-FS, DWI, and multiple phase T1 contrast). MR radiomics including features from all the sequences acquired showed higher accuracy than that of the radiologists (90.6% and 83.5%, respectively) [106]. Interestingly, in this study, the most common diagnostic error among the radiologists was the classification of borderline ovarian tumors into the benign group. Therefore, when borderline ovarian tumors were excluded, the radiologist's diagnostic performance in differentiating benign from malignant tumors was comparable to the computer's performance [106]. In the same paper, the authors aimed to assess whether MR radiomics could differentiate between type I and type II epithelial ovarian cancer, showing a model accuracy for this endpoint of 83% and an AUC of 85%. In this analysis, the authors also showed that the diagnostic performance was higher when features extracted from all the sequences were included [106]. Finally, the authors demonstrate that after scoring the features by the least absolute shrinkage and selection operator method (LASSO), the model divided patients into good and poor prognosis groups with an AUC of 0.899 and that T1-weighted imaging (WI) radiomics features were more likely associated with the clinical outcome than the other sequences [106]. Similarly, Jian et al. developed an MR combined radiomic model extracted from the combination of the four following sequences (T2WI-FS, DWI, ADC, and CE-T1WI) which were able to differentiate type I and type II epithelial ovarian cancer. This model achieved an AUC of 0.834 and 0.847 in internal and external validation cohorts, respectively [107].

With the aim of comparing the ability of clinical features, conventional MR image features, ADC value, T2WI, DWI, DCE- MR radiomics, and a combined multiple features model to predict the type of epithelial ovarian cancer, Qian et al. retrospectively evaluated 61 patients with epithelial ovarian cancer. In this study, the model included T2WI, DWI, and DCE-MRI, and a multisequence model. 1070 radiomics features of each sequence were extracted. Then, univariate analysis and LASSO were used to select important features. The authors demonstrated that the traditional model achieved the best diagnostic performance, while the diagnostic efficacy of the mixed model was slightly increased, thus concluding that the traditional model represents a noninvasive and reliable tool that can better distinguish EOC type I from EOC type II preoperatively [108].

Wang et al. proposed a classification model to identify ex vivo benign, malignant, and normal ovarian tissue [109]. The authors extracted 75 three-dimensional texture features from second harmonic generation images of human ovarian tissue from 31 patients, using radiomics-based feature extraction methods. Combining the minimum redundancy maximum relevancy feature selection method and a

tree-based pipeline optimization tool, they classified benign, malignant, and normal fresh ex vivo ovarian tissue, with performance values at AUC-ROC of 0.98, 0.96, and 0.94, respectively [109].

Proteomics

Proteomics is the analysis of the entire protein complement of a cell, tissue, or organism under a specific, defined set of conditions [110]. Proteomics can complement genomic analysis by uncovering pathways and processes of cancer biology to match with particular clinical phenotypes [111]. Pairwise analysis of proteomic and genomic data from the same tumor has shown that proteomics give added information beyond that elicited only through genomic analysis [112].

In ovarian cancer, an analysis of proteomics utility in predicting recurrence and survival time was performed by the PRotein-driven index of OVARian cancer (PROVAR) study team in 2013 [113]. PROVAR analyzed 412 ovarian cancer cases from TCGA [113]. They found that 5 proteins were associated with longer progression-free survival (PFS) and greater overall survival (OS), namely: androgen receptor (AR); phosphorylated tafazzin (pTAZ); BH3-interacting domain death agonist (BID); phosphorylated epidermal growth factor receptor (pEGFR); and 70 kilodalton heat shock protein (HSP70) [113]. Conversely, 4 proteins were highly expressed in patients with shorter PFS and shorter OS: signal transducer and activator of transcription 5 α (STAT5 α); phosphorylated protein kinase C-α (pPKCα); phosphorylated dual-specificity mitogen-activated protein kinase 1 (pMEK1); and eukaryotic translation elongation factor 2 (EEF2) [113].

Of the markers discovered in the PROVAR study, AR proved the most robust [113]. No change in its abundance was noted between the primary and metastatic tumors, which suggested that the downregulation of AR happens early in carcinogenesis [113].

The clinical proteomic tumor analysis consortium (CPTAC), in their 2016 study, used mass spectroscopy to categorize 174 ovarian tumors from TCGA [111]. They integrated previously sequenced genomic data from the TCGA study [114] with proteomic measurements to gain insight into the effect genomic copy number alterations (CNAs) had on the proteome. They found there was a convergence of CNA targets on a set of biological functions associated with motility/invasion and immune regulation, both classical of cancer cells [111]. They compared the presence of phosphorylated peptides in tumors of patients who survived < 3 years and those who survived > 5 years and found that PDGFR-beta (associated with angiogenesis), rhoA-regulatory, and integrin-like kinase pathways (both associated with cell mobility and invasion) were most abundant in short survivors [111]. The proliferation-associated transcription factor serum response factor (SRF) and the target proteins it regulates were also found to be more abundant in these short-surviving patients [111]. Their study found that combining analysis of protein quantity and phosphorylation status gave greater statistical significance when correlated with overall survival, emphasizing the utility of assessing protein phosphorylation in understanding pathway activity thus linking proteotype with phenotype [111].

Recent work has integrated proteomic analysis with CT-based qualitative and radiomic features [115]. In a retrospective hypothesis-generating study of 20 patients with HGSOC awaiting primary cytoreductive surgery, the abundance of certain proteins was found to be associated with CT-based qualitative traits, namely cysteine-rich protein 2 (CRIP2 – a tumor suppressor which regulates cell proliferation) was negatively correlated with mesenteric disease; and Melanoma Antigen Gene A4 (MAGEA4a—of the MAGE family, which are broadly expressed in many tumor types [116]) was positively correlated with supradiaphragmatic lymphadenopathy [115] (overexpression of MAGE is a predictor of poor PFS and OS in ovarian cancer [116–118]).

Texture feature extraction of intra-and inter-site heterogeneity (cluster-site entropy, cluster standard deviation, and cluster dissimilarity) was calculated and integrated with the proteomic data for those tumors. It showed an association between low levels of argininosuccinate synthase 1 (ASS1) and more heterogenous tumors [115]. This finding is in agreement with our knowledge of ASS1, low levels of which correlate with platinum therapy resistance and poor prognosis [119], and more heterogenous tumors, which are also predictive of worse survival [120].

Proteomics has the potential to facilitate the paradigm shift from treatment based on trial and error guided by anatomy and genetic profiling of tumors, to tailored, individualized treatment-based specifically on a tumors molecular profile [121]. To this end, large-scale prospective trials such as those planned by the APOLLO group (Applied Proteogenomics OrganizationaL Learning and Outcomes) will give greater insight into pathways of ovarian cancer and potential therapeutic liabilities and allow discovery and full validation of markers of disease heterogeneity, treatment resistance, and predictors of outcome [121]. Further large prospective studies integrating proteomic, genomic, and imaging tools are also necessary to potentiate the development of radiomic and radiogenomic tools towards true precision medicine [122].

Critics and challenges

Radiomics is in the early stages of development, with improvements to each step of the entire analytical process still required [123].

Firstly, one of its main limitations is the lack of standard protocol in terms of feature selection or model construction. A large number of feature selection algorithms and classifiers are available for use. An algorithm appropriate for a particular dataset might be inappropriate for another [124]. There is also great variety in the methods employed in most radiomic studies in ovarian cancer, with the frequent use of in house software raising issues for generalizability and reproducibility.

Secondly, feature reproducibility might be compromised when images are obtained from different vendors. CT features vary from one scanner to another depending on the parameters being used and from one reconstruction algorithm to another. In PET imaging, textural features are most sensitive to reconstruction algorithms and post-filtering level. In MRI, textural features depend on the field of view, magnetic field strength, slice thickness, and the contrast agent. Although image pre-processing is critical to achieving a level of homogeneity within data, thus overcoming the heterogeneity that can taint the quality of the samples being studied, there is no consensus regarding the protocol to be followed for image pre-processing [125–127].

Thirdly, most radiomics studies involve small cohorts, in disproportion to the dimensionality of the features, thus greatly increasing the risk of overfitting. Moreover, most studies do not test their models on an independent validation dataset, which has been reported to inflate the risk alpha. This is the case in the studies published on ovarian cancer, with the number of patients included ranging from 20 to 364. Most of these studies did not have a validation cohort [33, 102, 103, 105, 107, 109]. Institutions should work together in order to improve data sharing as this might be a useful way to conduct robust studies and increased the speed of radiomics adoption into routine clinical practice [84].

The emergence of artificial intelligence (AI) and its progressively wider impact on radiology may overcome some limitations of radiomics such as the need for manual "human" segmentation. AI algorithms are not only able to analyze the predefined segmentation but also directly analyze the images in order to automatically design its own radiomic features without underlying human evaluation. Moreover, AI offers a better capability of handling a massive amount of data compared with the traditional statistical methods.

Conclusion

Although many issues need to be addressed, radiomics is a potential game changer shifting radiology from the traditional visual analysis to a more objective and automated analysis. By integrating imaging biomarkers automatically derived from imaging data to clinical, genomics, and/or proteomics data, radiomics offers huge opportunities to better capture tumor behavior. Radiomics raises particular hope in ovarian cancer to better capture the whole disease heterogeneity and offer a new tool to predict tumor aggressiveness and response to therapy.

Compliance with ethical standards

Conflict of interest The authors declared that they have no conflicts of interest.

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