# Neoadjuvant Radiotherapy and Radiomics

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Radiotherapy (RT) represents one of the most effective anticancer agents, which can be used either alone or in combination with other strategies (surgery, chemotherapy, and immunotherapy). Neoadjuvant radiotherapy is currently used mainly in locally advanced rectal cancer and sarcoma and in a subset of non-small cell lung cancer and esophageal cancer, whereas in other diseases it is under investigation. Neoadjuvant strategy, specifically, represents a type of induction therapy usually given as a first step to shrink a tumor before the main treatment, usually surgery, is given. In this setting, radiotherapy can be used either alone or in combination with chemotherapy. Radiomics in the field of neoadjuvant Radiotherapy can help in the choice of the best subsequent and tailored treatment strategy.

radiomics neoadjuvant radiotherapy texture analysis

## 1. Texture Analysis in Neoadjuvant Radiotherapy—A Focus on Esophageal Cancer

A trimodal approach with neoadjuvant chemoradiotherapy (nCRT) followed by surgery is the treatment of choice in locally advanced esophageal cancer (EC).

A clinical evaluation of the response is made with different imaging techniques (MRI, CT, and PET) which can classify the response according to the RECIST criteria [1][2][3][4][5][6]. With these premises, radiomic analysis has been used in this setting with the aim to predict the response to neoadjuvant strategy [3].

In patients treated for locally advanced EC, temporal changes in tumor volume (before and after nCRT) were related to pathological response, although the predictive value of this parameter was modest, with no correlation with overall survival [1].

Sun et al. [3] found that several histogram parameters calculated on DCE-MRI can be used in evaluating and predicting the nCRT response.

CT images are mostly used to extract morphologic information of EC, but recent studies suggest that quantitative image features can provide additional information correlated to tumor response and prognosis [7][8][9].

On the other hand, metabolic imaging has been found to be more accurate in evaluating the response to nCRT. Most 18F-FDG PET studies in EC quantify metabolic tumor activity solely by using the maximum standardized uptake value (SUVmax) [10][11]. However, this approach does not characterize the total activity nor heterogeneity of

the 18F-FDG uptake for the entire tumor [12][13]. Recent studies suggest that spatial image information provides additional information than SUVmax [14][15][16][17].

It has been hypothesized that tumors could be rendered more homogeneous following treatment due to a reduction in cellular density and interstitial pressure and to normalization of the vasculature with improved intra-tumor perfusion and oxygenation [9]. Studies that performed imaging before and after treatment reported that tumor heterogeneity generally decreased following treatment [9][18]. Simoni et al. found that metabolic TV (MTV) in poor responders was significantly higher than in good responders (38.6 mL vs. 17.7 mL, $p = 0.02$) [19].

Yip et al. reported that delta-radiomics calculated within MTV60% were the least correlated with pathological response. Instead, temporal changes in tumor 18F-FDG distribution after nCRT assessed by delta-second-order radiomics (ΔRLM textures) were correlated to the OS [20].

In a study of Beukinga et al., the most predictive textural features were Long Run Low Gray-Level (LRLGLe)-PET and Run-Percentage (RP)-CT. LRLGLe-PET depends on long runs (coarse texture) with low gray levels and was higher (i.e., low and homogeneous 18F-FDG uptake) for complete responders and lower (i.e., high and heterogeneous 18F-FDG uptake) for incomplete responders, possibly due to tumor hypoxia and necrosis [21].

In a French study, Hatt et al. assessed the value of MTV, entropy, dissimilarity, high-intensity large-area emphasis, and zone percentage for the prediction of OS of 112 patients with EC who underwent definitive CRT or nCRT followed by surgery [22]. MTV and heterogeneity had a less prognostic value in EC (vs. non-small cell lung cancer), which was attributed to smaller overall volumes. The local dissimilarity parameter appeared most predictive for OS.

Current research is focused on a correlation between the biological tumor markers from pre-treatment tumor biopsies and F-FDG PET-based radiomic features. The prediction model from Beukinga et al. tried to correlate HER2 and the CD44 expression and F-FDG PET-based radiomic features in predicting a complete response (pCR) to nCRT; it showed promising ability to identify pCR [23]. Analysis of texture within tumors on medical imaging, such as CT, MRI, and PET, is emerging as a potential biomarker to predict prognosis and treatment response in patients with EC. These findings could increase our capability to predict and evaluate the nCRT response and optimize treatment planning.

## 2. Texture Analysis in Neoadjuvant Radiotherapy—A Focus on Lung Cancer

Lung cancer represents the leading cause of cancer death and its treatment rely on different strategies, often used in combination, such as radiotherapy, surgery, chemotherapy, and immunotherapy [24][25][26][27]. Medical imaging is pivotal in all the different phases of lung cancer management, from diagnosis to the evaluation of the efficacy of different approaches, as well as in the subsequent follow-up [28][29][30][31][32][33][34][35].

A significant body of literature is available regarding the role of textural analysis in lung cancer. Radiomic features have been used both for diagnosis (discrimination of malignant nature of lung nodules, histology prediction, and genomic analysis) and for outcome prediction, particularly after definitive chemo-radiotherapy (CT-RT) or stereotactic body radiation therapy (SBRT) [36][37][38][39][40][41][42][43][44][45]. On the other hand, few studies focused on neoadjuvant radiotherapy, possibly because of the controversial benefit of adding surgery after CT-RT [46][47]. The largest available series included 127 stage II–III NSCLC patients treated with neoadjuvant chemoradiotherapy (CT-RT) followed by surgical resection. Texture analysis was conducted on primary tumors with features extracted from planning CT. The endpoint of the analysis was a pathologic response and gross residual disease. Seven features (one shape feature, three second-order features, and three higher-order features) were predictive for pathologic gross residual disease (AUC > 0.6, *p*-value < 0.05) and one for pathologic complete response (one higher-order feature) (AUC = 0.63, *p*-value = 0.01). These features suggested that a spherical disproportionality of the primary tumor site (i.e., more complex shape) was a predictor of pathological response, while spherical tumors and tumors with large flat zones were more likely to be linked with residual disease [48]. The same group conducted another analysis on a similar population, analyzing also features from pathologic lymph nodes. Radiomics analysis was performed on 85 primary tumors and 178 lymph nodes with the same endpoints as above (pathologic response and gross residual disease). A mix of clinical variables and conventional and radiomic features were used to create a predictive model. The model built from the radiomic features was the best at predicting pathologic response (AUC 0.68, $p < 0.05$), while a mixed clinical and radiomic model was better performing for gross residual disease (AUC 0.73, $p < 0.05$). The authors concluded that the features extracted from the lymph nodes were more informative than those derived by primary tumors [49].

A small study analyzing PET-CT included 13 patients on a prospective clinical trial of trimodal therapy for resectable locally advanced NSCLC. A true texture analysis was not performed; however, pre- and post-chemo-radiotherapy SUV was not correlated with any clinical endpoint (pathologic complete response, PFS, and OS) [50].

Chong et al. performed a texture analysis on a mixed population with NSCLC treated with neoadjuvant chemo-radiotherapy (CT-RT) or neoadjuvant EGFR-inhibitor. Focusing on the CT-RT group, 28 patients were included in the study. A pre-operative CT was used for analysis, and the endpoint again was a pathologic response. In the univariate analysis, tumor volume, mass, kurtosis, and skewness were significant predictors of pathologic response, although only kurtosis maintained its significance in the multivariate analysis (OR 1.107, $p = 0.009$). ROC analysis showed that the AUC for kurtosis was 0.943 and that the optimal cut-off value of percent change of kurtosis for predicting pathologic response was less than −23 (sensitivity, 87.5%; specificity, 84.3%) [51].

More recently, Khorrami et al. conducted a textural analysis on 90 stage IIIA NSCLC patients treated with neoadjuvant CT-RT, followed by surgical resection. Pretreatment CT scans were used for features extraction. Patients were randomly split into two sets, one for training and one for testing.

Interestingly, the authors analyzed the features not only from primary tumors, but also from the peritumoral region (defined as a 15 mm dilation from primary nodule) to identify a possible predicting role of the tumor microenvironment.

Thirteen intratumoral and peritumoral radiomic texture features were found to be predictive of major pathologic response and were used to define a classifier with an AUC of 0.90 ± 0.025 within the training set, and an AUC = 0.86 in the test set. This signature was also predictive for OS (HR = 11.18, 95% CI = 3.17, 44.1; *p*-value = 0.008) and DFS (HR = 2.78, 95% CI = 1.11, 4.12; *p*-value = 0.0042) in the testing set. The combination of peritumoral and intratumoral features performed better than a clustering built only on intratumoral features.

The results of this study highlight that heterogeneous enhancement and disruption of textural patterns within and outside the nodules (better identified by Law Laplacian and Laws features) can predict not only response, but also patients' prognosis [52].

Identifying patients who respond completely to chemoradiation and who do not require additional invasive local therapy, also considering the controversial role of surgery in this scenario, is an unmet clinical need.

The intrinsic potential of texture analysis in predicting a response after neoadjuvant CT-RT is plain. However, available studies are not enough to consider radiomics as a ready and easily accessible clinical biomarker. Larger studies, with a higher number of patients and with external validation, are needed before radiomic analysis could be clinically implemented. Analyzing available data, a special attention in future research should be paid to nodal and peritumoral features, which are potentially even more predictive than primary tumor analysis.

## 3. Texture Analysis in Neoadjuvant Radiotherapy—A Focus on Sarcoma

Soft tissue sarcomas (STS) are a group of mesenchymal malignancies encompassing a wide array of distinct clinical entities, including over 50 different histological subtypes [53]. Due to their rarity and non-specific clinical presentation (mostly consisting of slowly-growing indolent swellings in limbs or trunk), a differential diagnosis with benign tumors is challenging and may result in a significant delay to curative treatment, consisting of wide surgical excision in absence of metastatic dissemination [53][54]. Furthermore, their intrinsic heterogeneity is also displayed by variable levels of genomic profile complexity and structural architecture, resulting in different clinical presentations and inconsistent responses to standard treatments [54][55][56]. Unfortunately, one among the major predictors of outcome in operable patients—tumor histological grading—may be underestimated by tumor biopsy [57]. This is a relevant issue, since tumor grade determination may guide treatment management: low-grade STSs may be treated with planned marginal excision, sparing patients from more extensive surgery [58], while detection of high-grade disease may serve as a decision criteria for pre-operative treatment intensification [59][60]. Moreover, while the additional benefit of adjuvant chemotherapy is questioned and limited to a subset of high-risk patients, no consensual criteria have been provided to define this population; clinical [61] and genomic [62] classifiers have been proposed, although their use have not been implemented in clinical practice yet.

Hence, there is an urgent need to identify novel and readily available biomarkers to improve diagnosis, predict the disease course, and possibly define a tailored pattern of care in patients at high risk of disease relapse [54]. Radiomics may provide a valuable source of information in STS patients. Due to its non-invasive nature, radiomics

may quickly discern benign from malignant lesions, timely addressing the need for further investigation; secondarily, it may provide an appropriate histopathologic grade determination on the whole tumor bulk, thus overcoming the limitations of tumor biopsy in accounting for intratumor heterogeneity; finally, identification of specific signatures correlated with outcome may allow prediction of relapse risk and eligibility for further interventions.

Improvement in differential diagnosis of malignancy have been reported by several authors [63][64]. In particular radiomics-based differentiation between soft-tissue lipoma and well-differentiated liposarcoma [65][66] was demonstrated despite similar radiologic and pathologic presentation, often requiring molecular analysis of MDM2 amplification status; interestingly, superior performance of a machine-learning classifier as compared to trained radiologists has been shown [67]. Similarly, radiomic features allowed to distinguish myxoma from myxofibrosarcoma [68] and atypical leiomyoma from uterine sarcoma [69][70][71].

Machine-learning algorithms proved also useful in the prediction of histopathologic grade. Using CT- or MRI-based radiomics, different signatures associated with high-grade disease were identified [72][73][74][75][76][77][78]; in some cases, integration with clinical features resulted in the establishment of a prognostic nomogram for risk stratification [74].

A radiomic approach may be used to improve prediction of patients' outcome. RM texture analysis alone [79][80] or combined with PET/CT metabolic data [81][82] was associated with metastatic relapse and specific signatures were identified for prediction of survival [83][84]. Radiomic analysis was also applied on surveillance MRI in patients undergoing follow-up after surgical resection [85], resulting in improved detection and characterization of local recurrence [86].

Concerning prediction of sensitivity to treatment, preliminary results reported adequate concordance between radiomic features and response to neoadjuvant chemotherapy [87] or chemoradiation [88], as well as exclusive chemotherapy in unresectable patients [85][89].

On the other hand, while radiomics analysis correlated with adipocytic maturation following neoadjuvant chemotherapy in myxoid/round cells liposarcomas, it occurred independently from the chemotherapy regimen and was not correlated with metastasis-free survival [90]; similarly, radiomics was insufficient to predict the response from hypofractionated pre-operative RT [91].

Despite promising preliminary results, no radiomic signature for sarcoma has been implemented to date in clinical practice. Multiple issues have been detected in the pathway to translation from exploratory analysis into standard of care, ranging from lack of external validation and replicability, consistency, and cost-effectiveness of the imaging biomarkers proposed at present [92]. While these shortcomings are partially motivated by the complex workflow and relevant technical requirements needed for the development and elaboration of radiomic signatures, further effort is required for successful translation into clinical use.

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