REVIEW ARTICLE

Imaging biomarkers in upper gastrointestinal cancers

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ABSTRACT
In parallel with the increasingly widespread availability of high performance imaging platforms and recent progresses in pathobiological characterisation and treatment of gastrointestinal malignancies, imaging biomarkers have become a major research topic due to their potential to provide additional quantitative information to conventional imaging modalities that can improve accuracy at staging and follow-up, predict outcome, and guide treatment planning in an individualised manner. The aim of this review is to briefly examine the status of current knowledge about imaging biomarkers in the field of upper gastrointestinal cancers, highlighting their potential applications and future perspectives in patient management from diagnosis onwards.

INTRODUCTION
The term “biomarker” refers to a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or biological responses to therapeutic interventions.1-3 Biomarkers can be derived directly from human biological samples (including blood or other biological fluids, tissues or cells) or biosignals detected by diagnostic imaging techniques (such as multidetector CT, MRI, ultrasound or PET), providing anatomical and/or functional parameters that correlate with histopathological or molecular data.4-7 Imaging biomarkers can be either quantitative (e.g. lesion diameter or volume, CT density, MR signal intensity, radiomics features, and any other biomarker whose magnitude can be expressed as a quantity value) or qualitative (e.g. pathological grading systems that can be expressed as ordinal rather than continuous quantitative data, such as clinical TNM staging, BI-RADS, LI-RADS, PI-RADS, C-RADS, and so on).5,9 Compared to “real” biological samples, imaging biomarkers have the advantage of being noninvasive (or minimally invasive) and easily obtainable, making them attractive for repeated testing and follow-up. In addition, while conventional biopsy captures only a fraction of tumour cells that may not be representative of the entire tumour, imaging biomarkers can capture the whole tumour heterogeneity, thus playing a potentially critical role into guiding biopsy or whenever biopsy is unobtainable.10-12

Due to the incremental diagnostic and prognostic value that imaging biomarkers can provide over conventional modalities (which, however, remain indispensable for the routine diagnostic workup of cancer patients), a great interest has arisen in the scientific and medical community in searching for biomarkers and building biobanks that may lead to more effective, patient-specific treatment. In this perspective, extensive research has recently been made in the field of radiomics, a discipline dealing with high-throughput extraction and analysis of quantitative features from diagnostic images that cannot usually be derived from visual assessment (including shape/size-, histogram- or filter-based texture analysis) and form the quantitative imaging expression of pathological processes that are also expressed by other “omics”, such as genomics, transcriptomics, metabolomics and proteomics.5,8

In this paper we will give a brief, yet hopefully explanatory overview of the current potential role of imaging biomarkers in the management of upper gastrointestinal cancers, with oropharyngeal, oesophageal, and gastric cancers as paradigm diseases.

OROPHARYNGEAL CANCER
Head and neck cancer is the seventh most frequent cancer and the ninth most frequent cause of cancer-related death, with a worldwide incidence of 550,000 cases and 380,000 deaths annually, of which 90% are squamous cell carcinomas (SCC) in the adult population.13,14 Most oropharyngeal cancers are diagnosed at a locally advanced stage, usually requiring multimodality treatment (including surgery, chemotherapy and/or radiation therapy), and the rate of locoregional recurrence is as high as 25–50% depending on the lesion site, making recurrence risk the...
greatest hurdle in improving survival rate. Moreover, tumour biology (with particular reference to human papillomavirus [HPV] positivity) plays a pivotal role in defining the prognosis and optimal therapeutic strategy for patients with head and neck SCC, with HPV+ oropharyngeal SCC being associated with a better overall survival. Therefore, a comprehensive assessment of disease extension (including primary tumour site and locoregional lymph nodes) at baseline and after treatment is mandatory, also in consideration that oropharyngeal and other head and neck SCC recurrences tend to occur at a locoregional level within the same volume of treatment.12–17

Although conventional multidetector CT and MR imaging performed with state-of-the-art equipment is the mainstay for diagnosis, staging and follow-up of patients with oropharyngeal SCC, morphologic imaging can be limited in detecting subtle disease or differentiating disease recurrence from benign post-treatment changes (e.g. after surgery and/or radiation therapy) that may obscure viable tumour tissue or mimic disease, and usually cannot provide per se any insight about prognosis, likelihood of early and/or sustained treatment response, or eligibility to patient-tailored target therapies.14,18–20 On the other hand, both standard CT and MRI data and those derived from more complex implementations of cross-sectional imaging can be joined to build specific radiomic signatures that can lead to improved patient stratification and potentially more person-centred therapy.21–23

Other functional imaging modalities such as dynamic contrast enhancement (DCE)-MRI, CT perfusion imaging and dual energy CT (DECT) can enable a quantitative evaluation of tumour vascularity that can be useful in the pre- and post-treatment setting.14,32 In general, highly vascular SCC tend to have a better treatment response compared to less vascular ones due to their greater sensitivity to radiation and better delivery of chemotherapeutic drugs, yet they may have poorer outcome due to a higher metastatic potential.14,33 In terms of grading, quantitative DCE-MRI parameters [Ktrans, Ve and the rate constant of contrast transfer (Kp)] allowed to discriminate among tumour, metastatic lymph nodes and normal tissue, with Ktrans and Ve values of normal tissue being significantly lower from those of nodes (p < 0.001) and primary tumours (p < 0.01), whereas Kp values of primary tumours were significantly higher from those of nodes (p = 0.001) and normal tissue (p = 0.002), respectively.23 Moreover, Baker et al reported that DCE-MRI can predict tumour response to target therapies with EGFR-targeted tyrosine kinase inhibitors, in conjunction with 18F-FDG PET.36

Among MRI techniques, diffusion-weighted imaging (DWI) is a powerful quantitative biomarker that can identify foci of residual disease as areas of restricted diffusivity of water molecules, due to cancer cells being densely packed with a relatively high nucleocytoplasmic ratio compared with non-neoplastic tissues. This allows overcoming potential confounding factors such as diffuse oedema and contrast enhancement as a result of inflammation and/or post-radiation sequelae, or faint or no enhancement in poorly vascularised and/or highly necrotic tumours, resulting in increased sensitivity in detection of primary oropharyngeal SCC.14,20 In a recent large meta-analysis, DWI-based apparent diffusion coefficient (ADC) quantitative assessment outperformed anatomical MRI for detection of primary tumour site with a pooled sensitivity and specificity of 89% and 86% vs 84% and 82%, respectively.23 Lower ADC values have also been found in malignant than in benign lymph nodes sized down to 5–10 mm, and Holzapfel et al were able to correctly classify cervical lymph nodes as benign or malignant using an ADC threshold of 1.02 × 10−3 mm2/s in 94.3% of cases.14,26,27 Furthermore, Hwang et al assessed the performance of standard (b = 1000 s/mm2) and high b-value (2000 s/mm2) DWI in differentiating between recurrent tumour and post-treatment changes, and found that the ratio between ADC2000 and ADC1000 was significantly higher in the former than in the latter (73.5% vs 56.9%, p < 0.001), with a cut-off value of 62.6% leading to a sensitivity, specificity, and diagnostic accuracy of 95.0%, 69.2%, and 84.8%, respectively.28 Of interest, patients with a good response to induction neoadjuvant chemotherapy were found to have lower ADC2000 values along with smaller tumour volume than poor responders, suggesting a potential role of high ADC values in predicting tumour response.29 In terms of risk stratification, it has been reported that the combination of poor prognostic factors such as high 18F-FDG PET-CT-derived SUVmaxT/B and high ADCmin values improves the prognostic role of the two separate parameters (with high ADCmin identifying SCC patients with worse prognosis among those with high SUVmaxT/B).30 Moreover, a significant association was observed between histopathological markers of tumour proliferation and ADC and SUV values calculated at simultaneous 18F-FDG-PET/MRI, with mean ADC being negatively correlated with Ki67 level (r = −0.728, p = 0.011) and total nucleic area (r = −0.691, p = 0.019), and combined SUVmax/ADCmin positively correlated with average nucleic area (r = 0.627, p = 0.039).31

Other functional imaging modalities such as dynamic contrast enhancement (DCE)-MRI, CT perfusion imaging and dual energy CT (DECT) can enable a quantitative evaluation of tumour vascularity that can be useful in the pre- and post-treatment setting.14,32 In general, highly vascular SCC tend to have a better treatment response compared to less vascular ones due to their greater sensitivity to radiation and better delivery of chemotherapeutic drugs, yet they may have poorer outcome due to a higher metastatic potential.14,33 In terms of grading, quantitative DCE-MRI parameters such as the blood volume transfer constant (Ktrans), the extracellular volume fraction (Ve), and the initial area under the curve (IUGC) were shown to be higher in poorly than in well-differentiated SCC, with Ktrans having the greatest diagnostic significance at a cut-off value of 0.270 min−1 and an overall diagnostic sensitivity and specificity of 95.0 and 90.9%.34 Chen et al found that DCE-MRI parameters [Ktrans, Ve and the rate constant of contrast transfer (Kp)] allowed to discriminate among tumour, metastatic lymph nodes and normal tissue, with Ktrans and Ve values of normal tissue being significantly lower from those of nodes (p < 0.001) and primary tumours (p < 0.01), whereas Kp values of primary tumours were significantly higher from those of nodes (p = 0.001) and normal tissue (p = 0.002), respectively.23 Moreover, Baker et al reported that DCE-MRI can predict tumour response to target therapies with EGFR-targeted tyrosine kinase inhibitors, in conjunction with 18F-FDG PET.36
Table 1. Summary of the features and main findings of the studies on imaging biomarkers in head and neck cancer (with particular reference to oropharyngeal cancer) cited in the text. Case reports and general reviews articles are not included. References are sorted in the order in which they appear in the text.

| Reference            | Tumour type and location | Imaging features | Main findings                                                                                                                                                                                                 |
|----------------------|--------------------------|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| van der Hoorn et al. | Head and neck SCC (oral, pharynx, larynx) | MRI, ADC         | Pooled analysis of anatomical MRI of the primary site showed a sensitivity of 88% (95% confidence interval 72−92%) and specificity of 89% (74−96%) and a pooled sensitivity of 89% (95% confidence interval 86−93%) and specificity of 89% (74−96%). ADC of the primary site showed a sensitivity of [0.70−0.80] and specificity of [0.70−0.80]. |
| Leijenaar et al.     | HPV+ oropharyngeal SCC   | Radiomic signatures (Mall, Mno art) | Diagnostic accuracy, OS: AUC for M_all and Mno art as high as 0.70−0.80. Consistent and significant split between survival curves with primary TV−35 cm and HPV status determined by p16 (p=0.007, HR 0.46), M_all (p=0.036, HR 0.55) and Mno art (p=0.027, HR 0.49). |
| Stronger et al.      | Oropharynx, hypopharynx and larynx | Primary tumour volume (TV) before CRT | PFS, OS: Better 5-year progression-free survival (PFS) and overall survival (OS) with primary TV <35 cm (71% vs 43%, p=0.01) and TV <35 cm, HR 0.24, p=0.0014. Longer PFS and OS with primary TV <35 cm (0.01−0.35, p=0.03−0.22 and 8.4±4.1, p=0.001, respectively). Primary tumour volume was a significant predictor of outcome (HR 0.48, p=0.048) and TV <35 cm and TV ≥35 cm (p=0.04, HR 1.28). |
| Kuno et al.          | Head and neck SCC (oropharynx, larynx, hypopharynx and oral cavity) | CT texture parameters | 3 histogram features (geometric mean, HR = 4.68, p = 0.026; harmonic mean, HR = 8.61, p = 0.004; fourth moment, HR = 5.72, p = 0.035) and four gray-level run-length features (short-run emphasis, HR = 3.75, p = 0.044; gray-level nonuniformity, HR = 5.72, p = 0.035; run-length nonuniformity, HR = 3.75, p = 0.044; short-run low gray-level emphasis, HR = 5.72, p = 0.035) were significant predictors of outcome after adjusting for clinical variables. |
| Feliciani et al.     | Head and neck SCC (oral cavity, oropharynx, hypopharynx, nasopharynx and larynx) | Pre-CRT 18F-FDG PET texture features | Local recurrence rates after CRT: Low-intensity long-run emphasis (LILRE) was a significant predictor of outcome regardless of clinical variables (HR <0.001, p=0.001). Better local failure prediction using multivariate model based on imaging biomarkers than that based on clinical variables alone (c-index 0.76 vs 0.65). |
| Holzapfel et al.     | SCC cervical nodal metastases | ADC              | Diagnostic accuracy for differentiating between benign and metastatic lymph nodes: ADC values of malignant lymph nodes were significantly lower than those of benign lymph nodes (0.878 ± 0.159 vs 1.110 ± 0.202, p<0.05). An ADC cut-off value of 0.924 × 10−3 mm2/s yielded a sensitivity of 82.7%, specificity of 85.2%, PPV 82.0%, NPV and accuracy of 85.6%, 87.4%, 80.7%, 85.2% and 82.0%, respectively for differentiating metastatic from benign lymph nodes (AUC 0.835). |
| Jin et al.           | Nasopharyngeal SCC cervical nodal metastases | ADC              | Diagnostic accuracy for differentiating between benign and metastatic lymph nodes: ADC values of malignant lymph nodes were significantly lower than those of benign lymph nodes (0.78 ± 0.09 vs 1.24 ± 0.16 mm2/s, p<0.05). An ADC cut-off value of 0.924 × 10−3 mm2/s yielded a sensitivity of 82.7%, specificity of 85.2%, PPV 82.0%, NPV and accuracy of 85.6%, 87.4%, 80.7%, 85.2% and 82.0%, respectively for differentiating metastatic from benign lymph nodes (AUC 0.835). |

(Continued)
| Reference          | Tumour type and location                                                                 | Imaging features | Endpoints                                                                 | Main findings                                                                                                                                                                                                 |
|--------------------|------------------------------------------------------------------------------------------|------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hwang et al. 28    | Head and neck SCC (oral cavity, oropharynx, sinonasal cavity, nasopharynx, hypopharynx, external auditory canal) | ADC              | Diagnostic accuracy for differentiating tumour recurrence from post-treatment (surgery and/or chemo/radiotherapy) changes | • Significantly lower ADC_{max} in recurrent tumour than in post-treatment changes ($p < 0.001$)  
• Significantly higher ADC_{max} in recurrent tumour than that in post-treatment changes ($73.5 \pm 7.2\%$ vs $56.9 \pm 8.8\%$, $p < 0.001$)  
• ADC_{max} was the only independently differentiating variable ($p = 0.024$)  
• An ADC_{max} cut-off value of 62.6\% yielded a sensitivity, specificity and accuracy of 95.0\%, 69.2\% and 84.8\%, respectively |
| Ryoo et al. 29      | Head and neck SCC (oral cavity, oropharynx, nasopharynx, supraglottic larynx, maxillary sinus) | ADC              | Diagnostic accuracy for predicting response to induction chemotherapy    | • Good responders had significantly lower ADC_{max} values than poor responders ($0.62 \pm 0.14$ vs $0.76 \pm 0.15 \times 10^{-3} \text{mm}^2/\text{s}$, $p = 0.02$)  
• Mean ADC_{max} was a significant predictor of response to induction chemotherapy at multiple logistic regression analysis ($p = 0.04$) |
| Preda et al. 30     | Head and neck SCC                                                                         | SUV, ADC         | DFS                                                                      | • Patients with SUV_{maxT/B} $\geq 5.75$ had an overall worse prognosis ($p = 0.003$)  
• Lymph node status- and diameter-adjusted SUV_{maxT/B} and ADC_{max} were significant predictors of DFS (HR = 10.37 and 3.26 for SUV_{maxT/B} $\geq 5.75$ and ADC_{max} $\geq 0.58 \times 10^{-3} \text{mm}^2/\text{s}$, respectively)  
• In patients with SUV_{maxT/B} $\geq 5.75$, high ADC_{max} was a significant predictor of worse prognosis (adjusted HR = 3.11) |
| Surov et al. 31     | Head and neck SCC                                                                         | SUV, ADC         | Tumour proliferation indexes (Ki67, cell count, total nucleic area, average nucleic area) | • ADC_{max} correlated with Ki67 level ($r = -0.728$, $p = 0.011$) and total nucleic area ($r = -0.691$, $p = 0.019$)  
• ADC_{max} correlated with Ki67 level ($r = -0.633$, $p = 0.036$)  
• Combined parameter SUV_{max}/ADC_{min} correlated with average nucleic area ($r = 0.627$, $p = 0.019$) |
| Dong et al. 34      | Head and neck SCC                                                                         | DCE-MRI (K\text{trans}, V\text{e}, \text{iAUC}) | Tumour grading                                                          | • Higher K\text{trans}, V\text{e} and iAUC in poorly differentiated than in well differentiated SCC ($p < 0.001$, 0.013 and <0.001, respectively)  
• K\text{max} had the greatest diagnostic significance, with a cut-off value of 0.270 min$^{-1}$ yielding a Youden index, specificity and sensitivity of 0.859, 95.0\% and 90.9\%, respectively |
| Chen et al. 35      | Head and neck cancer (nasopharynx, oropharynx, tongue base, larynx)                     | DCE-MRI (K_{max}, V_{e}, k_{ep}) | Differentiation among tumours, metastatic nodes and normal tissue      | • $K_{\text{max}}$ and $V_{e}$ of normal tissue ($0.159 \pm 0.087 \text{min}^{-1}$ and $0.229 \pm 0.146$) were lower than those of nodes ($0.332 \pm 0.149 \text{min}^{-1}$ and $0.408 \pm 0.124$, $p < 0.001$) and primary tumours ($0.251 \pm 0.066 \text{min}^{-1}$ and $0.344 \pm 0.081$, $p < 0.001$, respectively)  
• $k_{\text{ep}}$ values of primary tumours ($0.621 \pm 0.195 \text{min}^{-1}$) were significantly higher than those of nodes ($0.429 \pm 0.206 \text{min}^{-1}$, $p = 0.001$) and normal tissue ($0.420 \pm 0.170 \text{min}^{-1}$, $p = 0.002$) |

(Continued)
Table 1. (Continued)

| Reference | Tumour type and location | Imaging features | Main findings |
|-----------|--------------------------|-----------------|---------------|
| Baker et al. 36 | Head and neck SCC murine xenografts | R1 and R2 relaxation, functional MRI, relative [18 F-FDG] uptake | • Lower baseline R2* (58.2 ± 7.2 vs 70.6 ± 2.4 s⁻¹, p < 0.05) in pretreatment, with significantly lower Hoescalt 33342 uptake and greater pimonidazole-adduct formation in the CAL R cohort (48.8% vs 67.3%, p < 0.05) associated with significantly greater expression of EGFR in CAL R than in CAL S tumours (p < 0.05) in differentiating metastatic from benign lymph node (CAL R; AUC 0.720 vs 0.605, p < 0.01) | • Higher relative [18 F-FDG] uptake in the CAL R cohort (48.8% vs 67.3%, p < 0.05) associated with significantly greater expression of EGFR in CAL R than in CAL S tumours (p < 0.05) in differentiating metastatic from benign lymph node (CAL R; AUC 0.720 vs 0.605, p < 0.01) |
| Zhong et al. 37 | Lymph node metastases from head and neck SCC | Preoperative DWI and perfusion CT | • Lower mean ADC in metastatic than in benign nodes (0.849 vs 1.361, p = 0.046) and lower MTT (5.56 ± 0.10 vs 9.86 ± 3.23 s, p = 0.002) in metastatic than in benign nodes (mean ± SD): An ADC cut-off value of 0.980 ± 0.107 × 10⁻³ mm²/s yielded a sensitivity of 77%, a specificity of 86%, and an accuracy of 81% for differentiating metastatic from benign lymph nodes (CAL R; AUC 0.720 vs 0.605, p < 0.01) | • Higher relative [18 F-FDG] uptake in the CAL R cohort (48.8% vs 67.3%, p < 0.05) associated with significantly greater expression of EGFR in CAL R than in CAL S tumours (p < 0.05) in differentiating metastatic from benign lymph node (CAL R; AUC 0.720 vs 0.605, p < 0.01) |
| Lam et al. 40 | Head and neck SCC, primary and lymph node metastases | DECT image quality | • 65keV monochromatic images yielded optimal signal-to-noise ratio (p < 0.001) | • An iodine content cut-off of 2.45 mg/ml to diagnose nodal metastases had 85% sensitivity and 87.5% specificity (AUC 0.923) | • An iodine overlay cut-off <57.5 HU to diagnose nodal metastases had 90% sensitivity and 78% specificity (AUC 0.896) |
| Tawfik et al. 43 | Metastatic SCC cervical lymph nodes | DECT-derived iodine content and iodine overlay | • Iodine content was significantly lower for metastatic lymph nodes (2.34 ± 0.45 mg ml⁻¹) than for normal (2.86 ± 0.37 mg ml⁻¹) lymph nodes (p < 0.0001) | • An iodine content cut-off of 2.65 mg/ml to diagnose nodal metastases had 85% sensitivity and 87.5% specificity (AUC 0.923) | • An iodine overlay cut-off <57.5 HU to diagnose nodal metastases had 90% sensitivity and 78% specificity (AUC 0.896) |
| Foust et al. 2018 | Oropharyngeal SCC with nodal metastases | DECT-derived iodine content and iodine spectral attenuation slope | • Iodine content was significantly lower in metastatic than in nonmetastatic nodes (0.96 ± 0.28 vs 1.38 ± 0.38 mg ml⁻¹, p = 0.002) | • A nodal iodine threshold ≤1.3 mg ml⁻¹ showed a sensitivity of 84.6% and a specificity of 75.0% (AUC 0.893, p < 0.0001) | • A nodal iodine spectral attenuation slope threshold ≤1.95 showed a sensitivity of 84.6% and a specificity of 75.0% (AUC 0.893, p < 0.0001) |
Similarly, perfusion CT can quantify the vascularity of primary head-and-neck SCC by applying specific bio-mathematical models of tumour neoangiogenesis (Figure 1). Evidence exists that a) better treatment response can be usually be predicted at perfusion CT before the beginning of therapy in more perfused tumours, and b) early perfusion response to CRT can be assessed before the onset of morphological changes at conventional morphological imaging.37,38 On the other hand, DECT is emerging as an increasingly widespread imaging technique that can join the fast imaging time, high spatial resolution, and excellent morphological detail of multidetector CT with the possibility to collect functional data via material decomposition, allowing to calculate iodine content as a biomarker of tumour vascularity with a potentially lower overall radiation and contrast dose compared with standard single-energy CT imaging39 (Figure 2). DECT can be effective in improving the detection and local staging of primary tumours, with particular reference to N-staging, which is often limited due to small and/or morphologically indeterminate lymph nodes leading to inconclusive findings at conventional anatomical imaging.38,40–42 To this regard, Tawfik et al reported significant differences in DECT-derived iodine content and overlay among normal, inflammatory and metastatic SCC lymph nodes.43 Moreover, DECT showed lower iodine content and spectral attenuation slope in metastatic oropharyngeal SCC than in non-neoplastic cervical lymph nodes, in line with the finding of a different intranodal iodine distribution that reflects pathological structure.44,45

Overall, the integration of quantitative image biomarkers in the diagnostic workup of patients with oropharyngeal cancer and other tumours of the uppermost portion of the digestive tract looks promising in an effort to optimise lesion detection and staging, either at primary sites (especially in case of suspected disease recurrence, when diagnosis by conventional imaging is often hampered by gross post-treatment sequelae) and at lymph node levels (possibly overcoming the poor performance of standard morphological imaging in differentiating smaller benign from metastatic lymph nodes and guiding the choice towards more or less aggressive lymph node resection). Moreover, the correlation between imaging biomarkers and the biological features of tumours (related e.g. to lesion aggressiveness) may be of great value to improve patient selection for the best possible treatment in an individualised fashion.

OESOPHAGEAL AND GASTRIC CANCER

Oesophageal cancer is the eighth most common cancer and the sixth most common cause of cancer-related deaths worldwide, accounting for more than 509,000 deaths in 2018.46 While initial staging of oesophago-gastric cancer is usually performed with contrast-enhanced CT, multimodality imaging with endoscopic ultrasound and 18F-FDG PET is useful to define local disease extent and rule out metastatic spread in patients being considered for curative treatment, in an effort to reduce futile surgery.47 MRI is a less routinely used, yet valuable tool that can reveal the detailed anatomic structure of the oesophagus, differentiating among the various wall layers for proper local staging and providing an accurate assessment of lesion length before and after radiation therapy.48,49

Table 1 (Continued)
Several imaging biomarkers have been identified that can help predict response of oesophageal cancer to CRT (Table 2). In this latter setting, Aoyagi et al reported that ADC values were significantly higher in patients with better survival rates, whereas in a recent meta-analysis the variation of ADC before and after treatment and post-treatment ADC were found to have good performance for evaluating CRT response. Furthermore, van Rossum et al showed that a treatment-induced relative increase in ADC during the first 2–3 weeks of neoadjuvant CRT for oesophageal cancer was highly predictive of histopathologic response, and also AUC changes at DCE-MRI were predictive of complete pathological response to neoadjuvant CRT at a threshold of −24.6% with sensitivity, specificity, positive and negative predictive values of 83%, 88%, 71% and 93%, respectively.

In parallel, a comparative study of DECT and standardised iodine concentrations in patients with oesophageal cancer before and after CRT showed a significant reduction of tumour normalised iodine concentration on iodine maps in responders, allowing to functionally evaluate treatment response and prognosis in terms of reduced tumour iodine uptake. Radiomics approaches have also recently been proposed for preoperative prediction of lymph node metastasis and tumour response to CRT in patients with oesophageal cancer, and of note, it has emerged that radiomics features can outperform size criteria in discriminating lymph node metastasis in resectable oesophageal SCC.

Gastric cancer is the fourth most common malignancy and the second most common cause of cancer-related death worldwide (738,000 deaths annually), whose prognosis and survival rate are poor in advanced stage disease and for which only...
Table 2. Summary of the features and main findings of the studies on imaging biomarkers in oesophageal cancer cited in the text. Case reports and general reviews articles are not included. References are sorted in the order in which they appear in the text.

| Reference | Tumour type and location | Imaging features | Endpoints | Main findings |
|-----------|--------------------------|------------------|-----------|--------------|
| Ge et al. | Oesophageal cancer | Pre- and post-CRT DECT-derived normalised iodine concentration (NIC) and normalised CT (NCT) values | Comparison of pre- and post-CRT NIC and NCT values obtained in the arterial (NIC-A, NCT-A) and portal venous phases (NIC-V, NCT-V) in good and poor responders | • Post-CRT NIC-A, NIC-V, NCT-A and NCT-V values were significantly lower than before CRT in good responders (0.23 ± 0.05 vs 0.28 ± 0.05, 0.49 ± 0.06 vs 0.54 ± 0.06, 0.27 ± 0.04 vs 0.34 ± 0.06, 0.50 ± 0.04 vs 0.57 ± 0.80, respectively; p < 0.05) • Post-CRT NIC-A, NIC-V, NCT-A and NCT-V values were significantly lower in good than in poor responders (0.23 ± 0.05 vs 0.29 ± 0.06, 0.49 ± 0.06 vs 0.51 ± 0.06, 0.27 ± 0.04 vs 0.31 ± 0.04, 0.50 ± 0.04 vs 0.54 ± 0.05, respectively; p < 0.05) • Post-CRT NIC-V and NCT-V values in poor responders were significantly lower than before CRT (0.51 ± 0.06 vs 0.56 ± 0.06 and 0.54 ± 0.05 vs 0.59 ± 0.04, respectively; p < 0.05) |
| Guo et al. | Oesophageal cancer (SCC, adenocarcinoma, small cell carcinoma) | CT, ADC | Diagnostic accuracy before treatment, outcome prediction during and after radiotherapy in CR and PR patients | • Significantly greater difference in length of oesophageal lesions measured at CT (1.15 ± 0.39 cm) than at DWI (from 0.19 ± 0.36 cm at b = 600 mm²/s to 0.84 ± 0.53 cm at b = 1000 mm²/s) compared with pathological specimens (p < 0.05) • Higher diagnostic rate at DWI than at CT (98.72% vs 88.46%, p = 0.022) • After radiotherapy, the clinical control rate and 3-year survival rate in the high ADC value group were higher than in the low ADC value group (90.24% vs 67.57%, p = 0.028 and 58.4% vs 32.43%, p = 0.037, respectively) • In the second week during radiotherapy and at the end of radiotherapy, the ADC values in the CR group were significantly higher than in the PR group (p < 0.05) • ADC values measured in the second week during radiotherapy and at the end of radiotherapy had an AUC of 0.776 and 0.935, respectively for predicting the CR rate of radiotherapy |
| Aoyagi et al. | Oesophageal SCC | Pre-CRT ADC | Prediction of CRT response or prognosis | • Higher ADC values were associated with CRT response (1.27 ± 0.17 vs 0.92 ± 0.28×10⁻³ mm²/s, p < 0.01) • ADC values higher than the average ADC of oesophageal cancer tissue (1.10 × 10⁻³ mm²/s) were associated with a higher survival rate (median OS according to ADC of 309 vs 197 days, p = 0.02) |
| Cheng et al. | Oesophageal cancer | ADC [ADC variation before and after CRT (ΔADC), post-ADC] | Prediction of early response to CRT | • ΔADC showed a pooled sensitivity, specificity, diagnostic odds ratio, and AUC of 93%, 85%, 78 and 0.91 • Post-ADC showed a pooled sensitivity, specificity, diagnostic odds ratio, and AUC of 79%, 90%, 26 and 0.85 |
| van Rossum et al. | Oesophageal cancer (adenocarcinoma, SCC) | ADC [ADC variation during treatment (ΔADC) during] | Prediction of pathologic response to neoadjuvant CRT | • ΔADC was significantly higher in patients with vs without pathologic CR (3.46±10.7% vs 14.0±13.1%, p = 0.016) and in good vs poor responders (30.5±8.3% vs 9.5±12.5%, p = 0.002) • ΔADC was predictive of residual cancer at a threshold of 29% (sensitivity, specificity, PPV and NPV of 100%, 75%, 94% and 100%, respectively) • ΔADC was predictive of poor pathologic response at a threshold of 21% (sensitivity, specificity, PPV and NPV of 82%, 100%, 95% and 80%, respectively) |

(Continued)
| Reference          | Tumour type and location                                    | Imaging features               | Endpoints                                                                 | Main findings                                                                                                                                 |
|--------------------|-------------------------------------------------------------|--------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Heethuis et al.⁵³  | Oesophageal cancer (SCC, adenocarcinoma, adenosquamous carcinoma) | DCE-MRI [change of AUC before neoadjuvant CRT (AUCpre), at 2–3 weeks during neoadjuvant CRT (AUCper), and after neoadjuvant CRT before surgery (AUCpost)] | Prediction of pathologic response to neoadjuvant CRT | • The difference between AUCper and AUCpre was most predictive for good response at a threshold of 22.7% (sensitivity, specificity, PPV and NPV of 92%, 77%, 79% and 91%, respectively)  
• The difference between AUCpost and AUCpre was most predictive for pathologic complete response at a threshold of −24.6% (sensitivity, specificity, PPV and NPV of 83%, 88%, 71% and 93%, respectively) |
| Shen et al.⁵⁴     | Lymph node metastases from oesophageal cancer                | CT radiomics features          | Prediction of lymph node metastasis status in the preoperative setting | • Significant association between radiomics signature and lymph node metastasis ($p < 0.001$), with an AUC of 0.806 and 0.771 in the training and validation cohort, respectively  
• Good discrimination of the predictive nomogram model (Harrell’s Concordance Index of 0.768 and 0.754 in the training and validation cohort, respectively) |
| Hou et al.⁵⁵      | Oesophageal carcinoma                                      | CT radiomics features          | Prediction of CRT response                                              | • Five radiomics features (Histogram2D_skewness, Histogram2D_kurtosis, GLSZM2D_LZE, Gabor2D_MSA-54, Gabor2D_MSE-54) discriminated nonresponders from responders (AUCs 0.686–0.727)  
• Two features (Histogram2D_skewness and Histogram2D_kurtosis) allowed differentiating SDs from PRs ($p = 0.015$ and $p = 0.039$, respectively)  
• One feature (Histogram2D_skewness) allowed differentiating SDs from CRs ($p = 0.027$)  
• Both ANN and SVM models had high accuracy for potentially predicting treatment response (ANN 0.972, SVM 0.891) |
| Hou et al.⁵⁶      | Oesophageal SCC                                             | MRI radiomics features (T2w, SPAIR T2w) | Prediction of CRT response                                              | • CRs vs SDs, PRs vs SDs, and responders (CRs and PRs) vs nonresponders (SDs) could be differentiated by 26, 17, and 33 features (T2w: 11/11/15, SPAIR T2w: 15/6/18), respectively  
• Prediction models (ANN and SVM) based on features extracted from SPAIR T2w sequences showed higher accuracy than those derived from T2w sequences (SVM 0.929 vs 0.893 and ANN 0.883 vs 0.861, respectively) |
| Tan et al.⁵⁷      | Lymph node metastases from resectable oesophageal SCC       | CT radiomics features          | Diagnostic accuracy                                                      | • The radiomics signature including five features was significantly associated with lymph node metastasis  
• The radiomics nomogram incorporating the signature and CT-reported lymph node status (i.e. size criteria) distinguished lymph node metastasis with an AUC of 0.758 and 0.773 in the training and test set, respectively  
• Discrimination of the radiomics nomogram exceeded that of size criteria alone in both the training ($p < 0.001$) and test sets ($p = 0.005$)  
• Integrated discrimination improvement (IDI) and categorical net reclassification improvement (NRI) showed significant improvement in prognostic value when the radiomics signature was added to size criteria in the test set (IDI 17.3%, $p < 0.001$; categorical NRI 52.3%, $p < 0.001$) |

CR, complete response; PR, partial response; SD, stable disease.
Table 3. Summary of the features and main findings of the studies on imaging biomarkers in gastric cancer cited in the text. Case reports and general reviews articles are not included. References are sorted in the order in which they appear in the text.

| Reference       | Tumour type and location                                                                 | Imaging features                                                                 | Endpoints                                                                 | Main findings                                                                                                                                                                                                 |
|-----------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Giganti et al.  | Resectable gastric cancer (adenocarcinoma, signet-ring cell carcinoma)                    | ADC                                                                              | Association between ADC and clinicopathological factors (i.e., pathologic T and N stages, tumour location, surgical approach, histologic subtype)          | • ADC values ≤ $1.5 \times 10^{-3} \text{ mm}^2/\text{sec}$ were associated with a negative prognosis in the total population (log-relative risk 1.73, standard error 0.56, $p = 0.002$) and in the surgery-only (log-relative risk 1.97, standard error 0.66, $p = 0.003$) and chemotherapy (log-relative risk 2.93, standard error 1.41, $p = 0.03$) groups  
• ADC values ≤ $1.5 \times 10^{-3} \text{ mm}^2/\text{sec}$ were associated with other significant prognostic factors, especially pathologic T and N stages ($p < 0.001$ and $p < 0.017$, respectively) |
| Liu et al.      | Gastric cancer (tubular or papillary adenocarcinoma, poorly cohesive adenocarcinoma, signet-ring cell carcinoma) | CT texture parameters in the arterial (AP) and portal venous phase (PVP)         | Diagnostic accuracy and correlation between preoperative CT texture parameters and pathological stage | • Maximum frequency in the AP and mean, maximum frequency, mode in the PVP correlated positively with T stage, N stage, and overall stage ($p < 0.05$)  
• Entropy in the PVP correlated positively with N stage ($p = 0.009$) and overall stage ($p = 0.032$)  
• Skewness in the AP had the highest AUC (0.822) in identifying early from advanced gastric cancers  
• At multivariate analysis four parameters (maximum frequency, skewness, entropy in the PVP, and differentiation degree from biopsy) allowed prediction of lymph node metastasis, distinguishing gastric cancers with and without lymph node metastasis with an AUC of 0.892 |
| Liu et al.      | Gastric cancer (tubular adenocarcinoma, papillary adenocarcinoma, poorly cohesive adenocarcinoma, signet-ring cell carcinoma, mucinous carcinoma, mixed types) | CT texture parameters                                                             | Prediction of histopathological characteristics                           | • Mean attenuation, maximum attenuation, all percentiles and mode derived from PVP images correlated significantly with differentiation degree and Lauren classification ($r = -0.231 \sim -0.324, 0.228 \sim 0.321$, respectively; $p < 0.05$)  
• Standard deviation and entropy derived from AP images correlated significantly with Lauren classification ($r = -0.265 \sim -0.222$, respectively; $p < 0.05$)  
• Standard deviation and entropy on AP images were significantly lower in cancers with than without vascular invasion ($p = 0.035$ and $p = 0.031$, respectively)  
• Minimum attenuation on AP images was significantly higher in cancers with than without vascular invasion ($p = 0.028$) |
| Liu et al.      | Gastric cancer                                                                         | CT texture parameters                                                             | Correlation between CT texture parameters and immunohistochemical markers (E-cadherin, Ki67, VEGFR2 and EGFR) | • Standard deviation, width, entropy, correlation and contrast from AP and PVP were significantly correlated with E-cadherin expression level ($p < 0.05$)  
• The skewness from the AP and the mean and autocorrelation from the PVP were negatively correlated with Ki67 expression level ($p < 0.05$)  
• Width, entropy and contrast from the PVP were positively correlated with VEGFR2 expression level ($p < 0.05$)  
• CT texture analysis had an AUC of 0.612\sim 0.715 for predicting E-cadherin, Ki67 and VEGFR2 expression levels |

(Continued)
### Table 3. (Continued)

| Reference     | Tumour type and location          | Imaging features                   | Endpoints                                                                 | Main findings                                                                                                                                                                                                 |
|---------------|----------------------------------|------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kim et al.    | Advanced gastric cancer          | CT texture parameters              | Prediction of occult peritoneal carcinomatosis (PC) detected at surgery     | • Patients with occult PC showed significantly higher average, entropy, standard deviation, and lower correlation ($p < 0.004$ for all)  
• Entropy was a significant independent predictor for occult PC, with a cut-off value $>7.141$ applied to the validation cohort yielding $80\%$ sensitivity and $90\%$ specificity for prediction of occult PC |
| Li et al.     | Gastric cancer following curative resection | CT radiomics features              | Prognosis prediction                                                       | • The radiomics nomogram incorporating the radiomics signature and significant clinicopathological risk factors (T stage, N stage, and differentiation) exhibited significant prognostic superiority over clinical nomogram and radiomics signature alone (Harrell concordance index of $0.82 \pm 0.71$ and $0.82 \pm 0.74$, respectively; $p < 0.001$)  
• Five radiomics features associated with prognosis were correlated with at least one clinicopathological characteristic, including differentiation, tumor size, N stage, TNM stage, and neural invasion (Spearman’s rho coefficient $0.28–0.38$, $p < 0.05$) |
| Li et al.     | Locally advanced gastric cancer  | CT radiomics signature             | Outcome prediction of neoadjuvant chemotherapy                             | • One cross-combination machine-learning method derived from AP images had an AUC $>0.6$  
• 12 cross-combination machine-learning methods derived from PVP images had an AUC $>0.6$  
• A feature selection method based on linear discriminant analysis + random forest classifier achieved a significant prognostic performance for PVP images (AUC $0.722 \pm 0.108$, accuracy $0.793$, sensitivity $0.636$, specificity $0.889$, $p = 0.041$) |
| Jiang et al.  | Gastric adenocarcinoma           | CT radiomics signature derived from PVP images | Prediction of survival and response to chemotherapy                       | • A radiomics signature consisting of 19 selected features was significantly associated with DFS (HR $1.744$, $p < 0.0001$) and OS (HR $3.308$, $p < 0.0001$) and was as independent prognostic factor  
• Incorporating the radiomics signature into the radiomics-based nomograms resulted in better performance for the estimation of DFS and OS than TNM staging and clinicopathological nomograms ($p < 0.0001$)  
• Stage II and III patients with higher radiomics scores exhibited a favorable response to chemotherapy |
| Caivano et al.| Gastric adenocarcinoma           | Preoperative ADC                   | Diagnostic accuracy compared to conventional MRI with pathology as gold standard | • Gastric cancer tissue had lower ADC values than normal gastric walls ($0.811 \pm 0.300$ vs $1.503 \pm 0.430 \times 10^{-3} \text{mm}^2/\text{s}$, $p < 0.05$)  
• Metastatic lymph nodes had lower ADC values than nonmetastatic lymph nodes ($1.70 \pm 0.40$ vs $2.10 \pm 0.22 \times 10^{-3} \text{mm}^2/\text{s}$, $p < 0.05$)  
• The T factor accuracy of conventional MRI and DWI was $73\%$ and $80\%$, respectively  
• The N staging accuracy of conventional MRI and DWI was $80\%$ and $93\%$, respectively |
| Joo et al.    | Gastric cancer                   | MRI with and without DWI, CT       | Diagnostic accuracy for preoperative staging with pathology as gold standard | • For N staging, MRI with DWI demonstrated higher sensitivity, but lower specificity ($86.7\%$ and $58.8\%$, respectively) than MRI without DWI ($90.0\%$ and $94.1\%$) or CT ($43.3\%$ and $100\%$) ($p < 0.05$) |
| Reference          | Tumour type and location | Imaging features | Main findings | Endpoints                          | Correlation between ADC and HER2 expression |
|--------------------|--------------------------|------------------|---------------|------------------------------------|---------------------------------------------|
| He et al.           | Gastric cancer           | ADC              | • Significant correlation between mean ADC values and HER2 status ($r = 0.312, p = 0.037$) and scores ($r = 0.419, p = 0.004$) |
|                    |                          |                  | • Mean ADC values of HER2+ cancers were significantly higher than those of HER2- tumours ($1.211 \times 10^{-3}$ vs $0.984 \times 10^{-3}$ mm$^2$/s, $p = 0.020$) |
| Zongqiong et al.    | Gastric cancer           | Perfusion CT     | • BF was higher in poorly and moderately differentiated cancer than in well differentiated cancer ($138.59 \pm 38.09$ and $110.01 \pm 31.90$ vs $75.28 \pm 6.81$ ml/100 g/min, $p < 0.05$) |
|                    |                          |                  | • BV was higher in poorly and moderately differentiated cancer than in well differentiated cancer ($21.08 \pm 4.11$ and $18.18 \pm 5.62$ vs $9.01 \pm 0.94$ ml/100 g, $p < 0.05$) |
|                    |                          |                  | • PS was higher in poorly and moderately differentiated cancer than in well differentiated cancer ($57.50 \pm 13.28$ and $40.08 \pm 15.82$ vs $10.05 \pm 0.71$ ml/100 g/min, $p < 0.05$) |
| Zhang et al.        | Gastric adenocarcinoma   | Perfusion CT     | • PS was significantly higher in poorly than in moderately differentiated cancers ($16.471 \pm 9.003$ vs $9.558 \pm 5.422$ ml/100 g/min, $p = 0.04$) |
|                    |                          |                  | • PS was significantly correlated with lymphatic involvement (Spearman's rho coefficient $0.480$, $p = 0.038$) and pTNM stage (rho = $0.509$, $p = 0.026$) |
| Liang et al.        | Gastric mucosal cancer   | DECT (IC and NIC on AP and PVP images) | • Both AP and PVP NIC values were significantly higher in poorly differentiated than in moderately differentiated ($0.133 \pm 0.032$ vs $0.102 \pm 0.028$, $p = 0.005$ and $0.419 \pm 0.066$ vs $0.369 \pm 0.044$, $p = 0.013$) |
|                    |                          |                  | • Significant correlation between NIC and MVD (AP NIC $r = 0.542, p = 0.000$) and PVP NIC ($r = 0.530, p = 0.000$) |
| Meng et al.         | Gastric mucosal cancer   | DECT (IC and NIC on AP and PVP images) | • Significant difference between the high and low MVD groups with respect to PVP NIC ($p = 0.045$) |
|                    |                          |                  | • NIC and IC in AP had sensitivity of 71.43% and 88.89% in differentiating gastric cancer from normal gastric mucosa (NGM) and gastric inflammation (GI) |

Table 3. (Continued)
### Table 3. (Continued)

| Reference   | Tumour type and location                                                                 | Imaging features                                      | Endpoints                                                                 | Main findings                                                                 |
|-------------|------------------------------------------------------------------------------------------|-------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Pan et al.75 | Gastric cancer (adenocarcinoma, signet-ring cell carcinoma, mucinous adenocarcinoma)     | DECT (keV images, conventional kVp images, NIC)       | Diagnostic accuracy with pathology as gold standard                       | • Overall accuracies for T, N and M staging determined with keV images and conventional kVp images were 81.2%, 80.0%, 98.9% and 73.9%, 75.0%, 98.9%, respectively  
• Higher accuracy in N-staging using optimal keV images than conventional kVp images (sensitivity, specificity and accuracy of 90.7%, 67.9% and 82.9% vs 88.8%, 60.7% and 79.2%; p < 0.05)  
• NIC values were significantly different between differentiated and undifferentiated cancer both in AP (0.21 ± 0.08 vs 0.28 ± 0.16, p = 0.02) and PVP (0.54 ± 0.17 vs 0.46 ± 0.12, p = 0.01)  
• NIC values were significantly different between metastatic and nonmetastatic lymph nodes both in AP (0.22 ± 0.09 vs 0.13 ± 0.06, p < 0.001) and PVP (0.47 ± 0.14 vs 0.30 ± 0.12, p < 0.001)  
• A threshold value of 0.145 for AP NIC and 0.333 for PVP NIC yielded a sensitivity and specificity of 84.1%, 67.1% and 89.9%, 67.6%, respectively |
| Cheng et al.76 | Early and advanced gastric adenocarcinoma                                                | DECT [IC, NIC, curve slope ($\lambda_{HU}$) in the PVP and delayed phase (DP)] | Association with Ki-67 protein expression as a marker of cell proliferation | • DECT parameters were significantly lower in early than in advanced gastric cancers both in PVP (IC 19.36 ± 2.82 vs 21.25 ± 4.91 mg ml$^{-1}$; NIC 0.35 ± 0.11 vs 0.42 ± 0.12; $\lambda_{HU}$ 2.20 ± 0.43 vs 2.67 ± 0.63; p < 0.05) and DP (IC 16.89 ± 2.07 vs 19.10 ± 4.07 mg ml$^{-1}$; NIC 0.43 ± 0.06 vs 0.58 ± 0.14; $\lambda_{HU}$ 1.99 ± 0.35 vs 2.51 ± 0.68; p < 0.01)  
• DECT parameters were positively correlated with Ki-67 grade (Spearman rho 0.818, 0.753, 0.728 in PVP and 0.730, 0.745, 0.468 in DP, respectively; p < 0.01) |
In a multivariate analysis of 99 patients with contrast-enhanced CT for the assessment of lymph node metastasis, significantly higher sensitivity over conventional MRI or juvant chemotherapy, respectively), ADC values of $1.5 \times 10^{-3}$ mm$^2$/s or lower were associated with a negative prognosis along with pathologic T and N stages, suggesting an important role of DWI in outcome prediction. Overall, such findings seem to reflect a relationship between quantitative imaging biomarkers and different molecular tumour fingerprints that may be exploited to tailor treatment, and to this latter regard it is worth mentioning, for instance, that ADC values were found to correlate with HER2 status.

Perfusion CT and especially DECT can also give a relevant contribution to local staging and prognostic assessment of gastric cancer. Zongqiong et al showed a correlation between perfusion CT parameters (BF, BV and PS values) and the degree of differentiation of gastric adenocarcinoma, whereas Zhang et al reported a significant difference in the PS values between patients with or without lymphatic involvement ($p = 0.038$), different histological grades ($p = 0.04$) and TNM staging ($p = 0.026$). On the other hand, in Liang et al’s study DECT-derived normalised iodine content on arterial and portal venous phase acquisitions was higher in poorly differentiated gastric adenocarcinomas than in moderately differentiated tumours, along with a significant difference in portal venous phase normalised iodine content between tumours with high and low microvessel density, as determined by CD34 staining. Quantitative analysis of DECT imaging parameters for the gastric mucosa can be useful to differentiate malignant from benign gastric mucosal lesions, with iodine concentration and normalised iodine concentration in gastric cancer being significantly different from those in normal and inflammatory mucosa, showing a sensitivity and specificity of about 90% in differentiating gastric cancer from normal mucosa on portal venous phase images. More generally, DECT with monochromatic imaging and quantitative iodine concentration measurements has higher diagnostic accuracy than conventional single-energy CT for T and N staging of gastric cancer (81.2% and 80% vs 73.9% and 75%, respectively), with iodine concentration indexes differing significantly between differentiated and undifferentiated gastric carcinoma, and between metastatic and non-metastatic lymph nodes. The diagnostic potential of DECT may be pushed even further to a molecular level, with quantitative parameters (such as iodine concentration, normalised iodine concentration, and curve slope) showing a significant positive correlation with Ki-67 antigen expression as a marker of tumour proliferation and allowing to differentiate between early and advanced gastric cancer.

Based on the above considerations, the evidence collected so far shows that imaging biomarkers can provide a significant added value to conventional imaging for improving T and N staging of oesophageal and gastric cancers and predicting early response to neoadjuvant CRT and overall prognosis. This might play a pivotal role into identifying the best treatment strategy for patients on a case-by-case basis [e.g. surgery with or without CRT, or neoadjuvant CRT? which degree of surgical radicality? which expected lesion aggressiveness (including conditions with a dramatic impact on treatment choice and prognosis, such as peritoneal dissemination)? any and which potential targets for specific therapies?], possibly leading to better patient outcomes, higher quality of life, and more effective use of healthcare resources.

**CONCLUSIONS**

Imaging biomarkers represent an exciting area of active research that can currently be considered a new frontier of oncologic...
imaging, owing to their potential to provide a substantial amount of additional information to guide all management steps of cancer patients (from lesion detection and staging to treatment planning, follow-up and prognostic assessment). In particular, the diagnostic workup of upper gastrointestinal cancers should significantly benefit from a combined and thorough analysis of available imaging biomarkers, due to the heterogeneous biological features of such diseases that usually require a complex diagnostic and therapeutic approach. It is likely that in the near future, a growing number of imaging biomarkers and radiomics features will reach the status of established diagnostic imaging criteria, possibly favouring treatment individualisation and improving overall patient outcome.

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