Review Article

Imaging in evaluation of response to neo-adjuvant treatment

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Abstract: Adenocarcinoma of the gastroesophageal junction (GEJ) has shown better overall prognosis when treated with neoadjuvant therapy prior to surgery; studies have demonstrated that preoperative administration of these therapies can double the median overall survival in comparison to surgery alone. Even though histology remains the gold standard for the evaluation of treatment response, there is the impelling need of a non-invasive tool which can predict early on patient response; identifying responder or non-responder status during (or even before) neoadjuvant therapy becomes fundamental. The few studies which specifically deal with the role of guideline endorsed computed tomography (CT) in assessing tumor response after neoadjuvant therapy specifically in patients with GEJ carcinoma have been inconclusive. Conventional CT, which evaluates dimensional criteria, and PET, used to assess in vivo metabolic response, currently used for diagnosis and staging may be used in conjunction with quantitative parameters derived from magnetic resonance imaging (MRI) or hybrid systems which reveal different aspects of tumour growth, biology and aid staging. Therefore, the unique characteristics of each modality may provide information to tailor-treatment based on response during neoadjuvant treatment. We provide a brief overview of imaging techniques used in clinical practice to evaluate GEJ tumor response and the use of radiomics as an additional quantitative diagnostic tool.

Keywords: Gastroesophageal junction (GEJ); imaging, neoadjuvant therapy; computed tomography (CT); magnetic resonance imaging (MRI); PET; radiomics; treatment response

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Introduction

Adenocarcinoma of the gastroesophageal junction (GEJ) is defined as a tumor which topographic center is within 5 cm proximal (or distal) to the anatomical cardia (1). Patients' prognosis after upfront surgery is poor, due to high rates of complications, systemic and/or local recurrences (2). Multicenter, randomized trials [CROSS trial (3,4), POET trial (5)] have demonstrated benefit in terms of overall survival (OS) and/or progression free survival (PFS) in patients with locally advanced GEJ adenocarcinoma treated with neoadjuvant chemoradiotherapy (nCRT). In particular, the CROSS trial (3,4) demonstrated that preoperative administration of nCRT doubled the median overall survival of locally advanced esophageal and GEJ neoplasms in comparison to surgery alone and that 29% of these patients had a complete pathological response, suggesting that a subgroup of patients did not benefit from surgery, also considering its known side effects. Conversely, 18% of patients who underwent nCRT were deemed as being non-responders and did not benefit from nCRT but only suffered its side effects.

The proper assessment of tumor response after nCRT is

therefore fundamental, but early definition of responder or non-responder status during (or even before) neoadjuvant therapy is even more important since it could enable tailored therapeutic plans, avoiding unnecessary treatment efforts and related adverse effects, with a major impact on patients' quality of life as well as health care costs.

Although histopathology remains the gold standard for evaluation of response to nCRT, in some cases intermediate biopsies do not always predict outcome. In the diagnostic cohort preSANO trial (6), TRG3/4 neoplasms were missed in eight out of 26 cases with endoscopy guided biopsies and fine needle aspiration (FNA) and in four out of 41 cases with bite on bite biopsies and FNA performed four to six weeks after nCRT completion. In addition to invasiveness, bioptic procedures also have the limitation not to provide a reliable depiction of the entire tumor heterogeneity.

There is indeed an urgent need to identify a non-invasive tool able to depict the tumor microenvironment as a whole in this clinical setting. Morphologic cross-sectional imaging can here play a lead role: according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (7), computed tomography (CT) has proven to be the most standardized, validated tool for tumor response assessment, based on dimensional comparison. However, its use may be limited especially when dealing with tumors with blurred contours and a consistent amount of fibrosis following nCRT, common feature in GEJ neoplasms (7). Additionally, it may become challenging to distinguish viable tumor from necrotic scar tissue (8), further increased by a clinically relevant delay between cell death and tumor shrinkage. The guideline endorsed imaging has therefore only limited role in assessing the actual benefit of nCRT in GEJ (7).

Functional imaging, such as positron emission tomography (PET), has also been evaluated as an alternative tool for evaluating tumor response, as it relies on a metabolic rather than a purely dimensional evaluation. An additional readily available imaging modality, magnetic resonance imaging (MRI) could allow collection of both morphologic and functional data (9), and act as a biomarker extraction tool. Unfortunately, in the past its broad use in the gastroesophageal tract has been precluded by technical difficulties.

Do solutions exist? In this article, the authors are providing data to support a proper choice of imaging techniques, including CT, MRI and PET, in this diagnostic dilemma. Examples of standard of care clinical practice, novel, quantitative diagnostic approaches, with a particular focus on radiomics, as well as the combination of different imaging modalities have been also reported

Methods

To evaluate the ability of the different available imaging techniques as non-invasive markers of treatment response, a literature review was conducted in a single publicly available database, MEDLINE (via PubMed). Two of the authors (VN, a third-year radiology resident, and PM, an experienced nuclear medicine physician) independently performed a computer-aided search for original articles not limited in the past, closed on March 1, 2020.

Study eligibility criteria

The review was based on PICOS (P: population, I: intervention, C: comparator, O: outcomes and S: study design) criteria. The population criteria were adults with GEJ adenocarcinoma, treated with nCRT or nCxT presenting with an imaging prior to and post treatment (and/or during treatment) and histology (intervention and comparator used as gold standard, respectively), regardless of stage and study design. A combination of the following words was used: "*gastroesophageal junction* or *esophagogastric junction* or *esophageal* or *esophagus*" and "*adenocarcinoma* or *cancer* or *tumor* or *neoplasm*" and "*neoadjuvant therapy* or *neoadjuvant chemoradiation therapy*" and "*response assessment or prediction or early response*" and one of the following "*MRI* or *PET* or *PET/CT or PET/MR or PET/MRI or FDG PET/CT or FDG PET/MR or FDG PET/MRI* (using slash or hyphen) or *radiomics*". Abstracts, case reports and case series, editorials, letters to editor, animal studies and articles not in English language were excluded.

Selection of literature

After removing non-pertinent articles and duplicates, reviewers read the abstracts for eligibility based on reviewers read the abstracts for eligibility based on (I) studies in patients with locally advanced GEJ adenocarcinoma, (II) presence of imaging assessment before and after nCxT or nCRT (with or without intermediate imaging evaluation) and (III) reporting comparison of imaging findings to histopathology on surgically resected specimen or ultrasound guided biopsy. Histopathology was considered the reference standard for the purpose of this review. The reference lists of all selected articles were searched to identify further relevant studies and all studies selected were

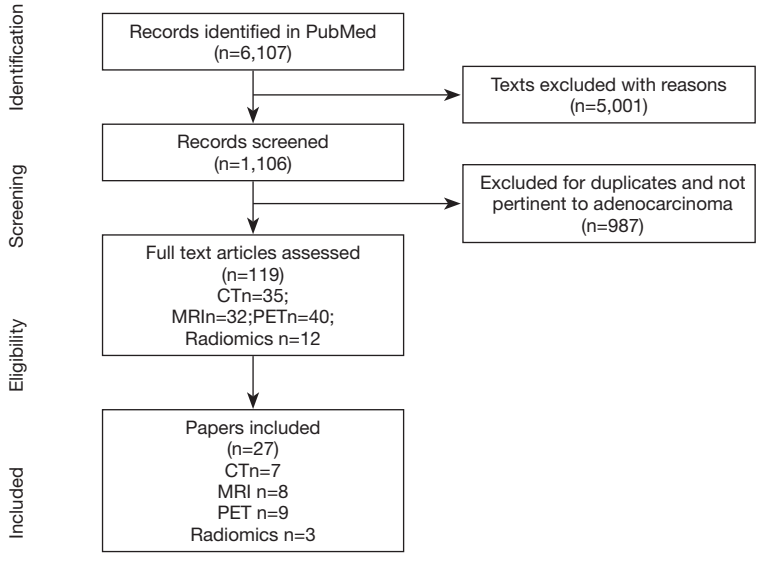

Figure 1 Flow diagram of article selection and exclusion process.

in adults regardless of prognosis and disease progression.

Results

The literature search resulted in a total of 6,107. After initial exclusions and screening (see *Figure 1*), 119 were considered eligible and 27 included in this review. Results are presented based on the different imaging modalities and on the radiomics approach. After removing non-pertinent records, exclusions and duplicates, 119 articles were found eligible. Results are presented based on the different imaging modalities and those evaluating radiomic features. In particular, seven papers met the inclusion criteria for CT, 8 for MRI, 9 for PET and 3 for radiomics.

CT

A major limitation of literature concerning the role of contrast enhanced CT in determining GEJ tumours response after nCRT/nCxT was that the majority of the studies meeting inclusion criteria considers at once both GEJ and oesophageal/gastric neoplasms, irrespective of different management strategies and prognosis.

Although changes in CT tumour volume demonstrated greater correlation with pathological response than changes in tumour diameter and were associated with lower interobserver variability (10), it is more technically demanding and only a modest predictor of pathological response at best (10-12). The cut offs values used for changes in tumour volume to differentiate responders from non-responders ranged from 10% to 20% (10,13). Some studies (11,13) did not find a significant correlation between CT volumetric changes and pathological response, with a non-optimal performance assessed by ROC (receiver operating characteristic) curves of 0.63 [95% confidence interval (95% CI), 0.45–0.82] (13).

CT showed a sensitivity ranging from 33% to 55% and a specificity from 50% to 71% (14) in predicting pathological response and TNM stage after nCRT. Many factors may influence such a low accuracy, the most important being that CT, is unable to adequately help differentiate between T1, T2 and T3 disease (14,15) due to a poor contrast resolution, thus downstaging the assessment. Perfusion techniques have shown to be useful in identifying histopathological responders which are reported to have a lower tumor permeability in comparison to non-responders (16). Radiation therapy, on the other hand, may induce the release of pro angiogenic factors and stimulate angiogenesis, thus impairing an optimal perfusion evaluation (14,15).

Early response assessment is heavily hampered by inflammation and tissue edema occurring during nCRT (14,15). Van Heijl *et al.* (13) observed a paradoxical increase of CT median tumor volume measured between baseline and 14 days after the beginning of nCRT in histopathological responders as well as in non-responders. Discordant results were observed in a cohort of 31 patients

with locally advanced GEJ neoplasms who underwent contrast enhanced CT scan before and two weeks after the beginning of nCxT (10), where early changes in CT tumor volume well predicted histopathological tumor response (sensitivity: 100%; specificity: 53%). In a large multicenter study evaluating combined endoscopy and CT (17), a good agreement was assessed between non-responders and histopathological response, with a very high negative predictive value (85–92%), even at interim assessment.

In another study using a CT perfusion scan, Lundsgaard Hansen *et al.* (16) reported a positive, significant correlation between an early decrease (after once cycle) in tumor permeability and overall clinical response after nCxT, based on dimensional criteria cut-off.

To our knowledge, no study specifically addresses the accuracy of CT in assessment of lymph node response after nCRT. In a cohort of 18 patients with esophageal or Siewert 1 GEJ neoplasms treated with either nCRT or nCxT, Giganti *et al.* (15) found that CT, relying on dimensional criteria alone, has low sensitivity and specificity (75% and 57%, respectively) in predicting N stage.

The selected studies assessing the role of CT in neoadjuvant treatment response in GEJ cancer are reported in *Table 1*.

MRI

Differently from CT imaging, MRI provides a multiparametric, multiplanar assessment of the tumor burden with high soft tissue characterization.

Recent literature (9) suggests that the use of MRI is becoming increasingly frequent in diagnosis and follow-up of GEJ tumors, mainly due to technical improvements (i.e., breath hold, cardiac gating sequences) and to the addition of new quantitative parameters [i.e., diffusion weighted imaging (DWI) and its corresponding reconstructed apparent diffusion coefficient (ADC) map, dynamic contrast enhanced (DCE) MRI], to purely anatomic (T1, T2 weighted) sequences, having an intrinsic high soft tissue contrast resolution enough to differentiate pathological wall layers. GEJ MRI requires minimal patient preparation to properly depict the multilayer pattern of the gastroesophageal tract; intramuscular scopolamine (in the absence of contraindications) results beneficial as does proper visceral distension through the administration of at least 500 mL of water after a 6-hour fasting (9).

DWI, based on the random Brownian motion of water molecules within a voxel of tissue, is sensitive to microstructural changes which occur earlier than anatomical changes during nCRT. In a prospective cohort of 32 patients with biopsy proven GEJ locally advanced tumors, De Cobelli *et al.* (22) found that a post treatment ADC absolute value higher than 1.84×10^{-3} mm^2/s and an increase of ADC percentage higher than 13.6% are useful findings in identifying pathological responders. The same authors demonstrated a strong inverse correlation between ΔADC (delta before and after nCRT) and tumor regression grade (TRG), regardless of any dimensional modification. A recent meta-analysis (23) including 236 patients substantially confirmed these observations (pooled sensitivity and specificity for ΔADC in predicting pathological response were 93% and 85%, respectively).

Similar imaging protocols have also shown to be able to differentiate responders from non-responders even after few cycles of nCRT. Weber *et al.* (24) used DWI-MRI to assess early response assessment of GEJ neoplasms, demonstrating that an increase in ADC absolute values after the first two weeks of nCRT was associated with 100% sensitivity and 50% specificity in identifying metabolic responders. A more recent meta-analysis (25) which includes 158 patients demonstrated that a relative increase of ADC values of approximately 21% after two to three weeks of neoadjuvant treatment correlates with favorable pathological response.

In a multicenter, international prospective study (26), patients scheduled to receive nCRT prior to resection were evaluated at three time points using DWI MRI scans (prior to, during and after nCRT). The authors found that relative changes in DWI parameters during nCRT were significantly different between responders and non-responders.

Giganti *et al.* (27) further explored the role of DWI in early prediction of responders and non-responders, using data from imaging prior to start of nCRT. The authors found that pathological responders have significantly lower pre-nCRT ADC absolute values than non-responders ($1.32\pm0.331\times10^{-3}$ *vs.* $1.47\pm0.407\times10^{-3}$ mm^2/s). Possibly, the biological rationale of such a finding is that the higher the cellularity, the lower the ADC values but also the greater cytotoxic effect.

DCE MRI allows quantification of tumor perfusion and permeability. In a cohort of 26 patients with locally advanced esophageal and GEJ neoplasms, Heethuis *et al.* (28) found that DCE MRI changes, evaluated throughout treatment in the so-called tumor area under the concentration time curve (AUC), well correlated with pathological response. The same authors recently reported (29) that combining DWI and

Table 1 Studies that assessed the role of CT in neoadjuvant treatment response in GEJ cancer

Study	Localization	No. patients	Histology	Neoadjuvant therapy	Timing of scans (post treatment)	Pathological assessment	CT parameters	Results
Early response								
Beer *et al.* (10)	GEJ cancer (Siewert I-II)	31 (21 with pathological assessment)	AC	CxT	• Baseline • Interim (day 14-17) • Prior to surgical resection (day 17/21)	Modified Mandard score [Becker (18)] • Grade 1 (0–10% residual tumor per tumor bed): histopathological R • Grade 2-3: NR	• Maximum tumor diameter • Semi automated tumor volume • Delta values of diameter and volume between among and between 3 time pointsA	• Statistically significant differences in tumor volume and diameter (P=0.009 and P=0.011) delta baseline *vs.* interim • Statistically significant decrease in mean tumor volume *vs.* mean tumor diameter (P<0.001), CT prior to surgery • Post CRT (mean 73 days between scans) • Low interobserver variability for volumetric evaluations • Cut off –13.2% for diametric changes and 14.8% for volumetric changes in differentiating R from NR, with a sensitivity of 100% and a specificity of 53% for volumetric changes • Cut off –13.2% for diametric changes and 14.8% for volumetric changes in differentiating R from NR, with a sensitivity of 100% and a specificity of 53% for volumetric changes
Van Heijl *et al.* (13)	EC and GEJ cancer	39	AC; SCC	CRT	• Baseline • Interim evaluation (day 15 during CRT)	Mandard score (19): R defined Grade 1 (complete response) and Grade 2 (<10% viable residual tumor cells)	3D volume	• Tumor volume increases in R and NR with relatively higher increase in the histopathological NR (22%), non-significantly different compared to NR (12%) • AUC for pathological response assessment using CT =0.63 (95% CI, 0.45–0.82) • ΔCT volume cut-off >10%: sensitivity 19%, specificity 92%, PPV 83%, NPV 36% • ΔCT volume cut-off >20%: sensitivity 8%, specificity 100%, PPV 100%, NPV 35%
Early and late response								
Lundsgaard Hansen *et al.* (16)	Gastric and GEJ cancer	28 (26 all scans)	AC	CxT	• Baseline • Interim evaluation (median20 days) • Post CxT (median 79 days; 6 days prior surgery)	Mandard score: R defined; Grade 1 and Grade 2	• Perfusion parameters: arterial flow, blood volume, permeability measured as ktrans • Tumor volume	• Clinical response was positively correlated to decrease in tumor permeability (P=0.03) after one and three cycles of nCxT. A cut-off of 25% has a sensitivity of 69% and a specificity of 58% • Histological response correlated with decrease in tumor permeability (P=0.03) and volume (P=0.03) only after 3 cycles of nCxT • Non-statistical difference in arterial flow and blood volume

Table 1 *(continued)*

Table 1 *(continued)*

Study	Localization	No. patients	Histology	Neoadjuvant therapy	Timing of scans (post treatment)	Pathological assessment	CT parameters	Results
Blank *et al.* (17)	Gastric and GEJ (Siewert I-II-III) cancer	686 Cohort A 184 Cohort B	AC	Ct	• Baseline • Interim evaluation (118 pt) after 4–6 weeks of Ct • Post NT	Becker regression score (18): histological response classified as TRG 1a (complete regression) and 1b (<10% residual tumor)	Clinical response: combination of CT parameters (decrease of maximal transverse diameter <50%) and Endoscopic parameters (decrease of the endoluminal tumor size of >75%)	• Accuracy between clinical response and histopathological TRG =85% in Cohort A and 92% in Cohort B for NR and 52% in Cohort A and 50% in Cohort B for R • Sensitivity, specificity, PPV and NPV for histopathological response respectively 60.5%, 80.2%, 51.9% and 85.2% in Cohort A and 66.7%, 85.4%, 50% and 92.1% in Cohort B • Cohort A: clinical response statistically significant for prognosis in all localizations; histopathological regression only in AEG I-II; clinical response was an independent prognostic factor (non-response HR for death 1.4; 95% CI, 1.0–1.8, P=0.032) • Cohort B: sensitivity of interim response *vs.* preoperative evaluation =84.4%, specificity 97.6%, PPV 93.3% and NPV 94.3% and statistically significant associated to survival (P=0.008); clinical response failed to reach statistical significance as independent prognostic factor
Late response								
Jones *et al.* (11)	EC	50	38 SCC; 12 AC	CRT	• Baseline • Post CRT (mean 73 days between scans)	America Joint Committee on Cancer Responders (20)	Responders = pCR	• Post CRT CT overstaged 36% and understaged 20% pathologic T classification • The post CRT: CT T classification did not correlate with the pathologic T classification (P=0.09) • CT had a sensitivity of 65% and a specificity of 33% in evaluating the pathological response (PPV 58% and NPV 41%) using ECOG solid tumor response criteria • No significant correlation between radiographic and pathological stage (P=0.83), tumor pCR status (P=0.22) or tumor histology (P=0.59) • No difference in tumor location or histology
Konieczny *et al.* (12)	EC and GEJ cancer	35 (20 EC; 15 GEJ)	25 AC; 10 SCC	CxT or CRT	• Baseline • Post nCT (4–5 weeks)	Mandard score (tumor regression grade defined only in 25/35)	-Tumor depth -Modified WHO/ RECIST for one dimensional measurement	• T stage correctly predicted in 12 of the 35 patients (34%) • The tumor regression grade predicted correctly in 8% (2/25) patients; the degree of regression was overestimated in 24% and underestimated in 68% • Complete CT response in predicting pCR: sensitivity 20%, specificity 96%, PPV 67%, NPV 75%, accuracy 74%
Swisher *et al.* (21)	EC and GEJ cancer (47 EC; 56 GEJ)	103	AC; SCC	CRT	• Baseline • 2–5 weeks after CRT	Responders <10% viable cells	Esophageal wall thickness (67/103 patients with both CTs)	• Sensitivity, specificity and accuracy for pathological NR was respectively 51%, 69% and 62% on post CRT evaluation (threshold of oesophageal thickness ≥14.5 mm) • Confirmed utility of PET, CT, and EUS to identify pathologic responders

EC, esophageal cancer; GEJ, gastroesophageal junction; CxT, chemotherapy; CRT, chemoradiotherapy; EUS, ecographic ultrasound; CT, computed tomography; PET, positron emission tomography; R, responders; NR, non-responders; pCR, pathological complete responders; PPV, positive prognostic value; NPV, negative prognostic value; AC, adenocarcinoma; SCC, squamous cell carcinoma; HR, hazard ratio.

DCE MRI parameters, a more accurate assessment of tumor response to neoadjuvant treatment may be assessed.

Table 2 tabulates the selected studies assessing the role of MRI in neoadjuvant treatment response in GEJ cancer.

PET

Fluorine18 fluorodeoxyglucose PET/CT (18F-FDG PET/CT) is a functional imaging modality that allows non-invasive characterization of physiologic and pathologic process. 18F-FDG PET/CT is very promising tool to assess *in vivo* metabolic response to therapy, as measured by tumor glucose metabolic treatment-induced changes. PET has been proposed as a quantitative measure of response to neoadjuvant therapy for patients with GEJ and esophageal carcinoma, both as end-of-treatment evaluation and as early assessment of response during treatment.

In the setting of evaluation at the end of treatment, Kauppi *et al.* (32) investigated the value of 18F-FDG PET/CT in predicting histopathological response, overall survival and disease survival. They evaluated 66 patients treated with nCxT for locally advanced carcinoma of the esophagus or GEJ. 18F-FDG PET/CT was performed before and after completion of neoadjuvant therapy, with standardized uptake value (SUV) being assessed for both scans to evaluate its relative change (SUVΔ%). Authors demonstrated that a change in baseline SUVΔ >67% was able to optimally predict histopathological response (sensitivity: 79% and specificity: 75%), being also associated with improved overall survival and disease-free survival.

Hernandez *et al.* (33) found a significant correlation between SUVmax response and histologic response in patients with locally advanced GEJ adenocarcinoma or gastric cancer. However, disease specific survival was only predicted by histopathologic response and tumour staging, but not by SUVmax.

Lately, Gabrielson *et al.* (34) found a significant reduction of standardized uptake ratio (SUR) in the primary tumour in histological responders compared to non-responders; furthermore, changes in SUR were significantly greater in responders following nCRT, but not following CxT alone.

Regarding the early assessment of response during treatment, Zum Büschenfelde (35) and his group carried on a prospective trial involving 56 patients with locally advanced adenocarcinomas of the GEJ who underwent 18F-FDG PET/CT before and 14 days after starting chemotherapy. The relevance of this trial relies on the possibility of using 18F-FDG PET as a tool for guiding treatment algorithm and provides changes in treatment strategy early in the course of chemotherapy.

Harustiak *et al.* obtained different results compared to Zum Büschenfelde (36). In order to assess the tumour early metabolic response to chemotherapy, 18F-FDG-PET/CT was performed before (PET1) and after (PET2) initiation of the first cycle of chemotherapy. Authors did not identify any association between median **Δ**SUL (SUV normalized to lean body mass) or median **Δ**TLG (total lesion glycolysis of the primary tumour) and histopathological response, thus concluding that 18F-FDG PET/CT does not predict histopathological response in patients with adenocarcinoma of the esophagus and GEJ after the first cycle of chemotherapy.

Similarly to the previous group, Schneider and colleagues (37) assessed the accuracy of 18F-FDG PET/CT in predicting the early pathologic response after neoadjuvant chemotherapy in 30 patients with locally-advanced gastric or GEJ cancer receiving nCxT. Metabolic response (defined as a decrease in SUV ≥35%) after nCxT was detected in 66.7% of patients, and among metabolic responders, 50% showed major and 50% minor pathologic regression. 18F-FDG PET/CT showed a sensitivity of 90.9%, specificity 47.3%, a positive predictive value 50%, a negative predictive value 90% and an accuracy of 63.3% as predictor of early response to neoadjuvant chemotherapy, having limited value in predicting overall pathologic response. However, the reliable detection of non-responders allowed the identification of those patients requiring an immediate change of therapy strategy (i.e., resection or modified multimodality therapy), similarly to zum Büschenfelde *et al.* (35).

Findlay *et al.* (38) investigated a different but interesting aspect regarding the possibility of using metabolic nodal stage (mN) and response (mNR) as new markers of disease progression, recurrence, and death in patients with esophageal or GEJ cancer undergoing neoadjuvant chemotherapy. The same group (39) performed a validation study on a cohort of patients with both esophageal and GEJ cancer, studied with 18F-FDG PET/CT before and after neoadjuvant chemotherapy. In patients undergoing successful resection, those without complete mNR presented worse prognosis (disease-free survival hazard ratio =2.46; P=0.004). Interestingly, these associations were independent of primary tumor metabolic, pathological response, and stage. The absence of complete mNR predicted recurrence or death at 1 and 2 years, with positive predictive values of 44.4% and 74.1%, respectively. This study suggests that

Table 2 Studies that assessed the role of MRI in neoadjuvant treatment response assessment in GEJ cancer

Study	Localization	No. patients	Histology	Neoadjuvant therapy	Timing of scans	Pathological assessment	MRI modality	MRI parameters	Results
Early and late response									
De Cobelli *et al.* (22)	EC, gastric and GEJ cancer: (7 EC; 16 gastric; 9 GEJ)	32	26 AC; 6 SCC	CxT or CRT	• Baseline • Post NT (median 10±3 days)	Mandard score (19): R: TRG 1-2-3	1.5 T MRI with DWI cardiac and respiratory gated sequences (b value 0-600 s/mm^2)	ADC (mean of ADC of each section of the tumor excluding necrotic area)	• No differences in tumor volume values between R and NR
								• Pre-NT ADC, post-NT ADC, ΔADC	• Significant differences were found evaluating ADC, with lower pre-NT values and significant increase after NT in R
								• Tumor volume: post-NT V, ΔV	• Highly significant strong inverse correlation between ΔADC and TRG values (r=–0.71; P=0.000004); no evidence of correlation between ΔV and TRG (r=–0.02; P=0.883)
									• Pre-NT ADC cut off <1.5×10^{-3} mm^2/s: R detected with a sensitivity of 35.29%, specificity of 60%, PPV of 50%, NPV of 50% and accuracy of 46.87%
									• ΔV cut-off of 57% decrease: R detected with a sensitivity of 35.29%, specificity of 66.66%, PPV of 55.54%, NPV of 47.16% and accuracy of 50%
									• Post-NT ADC cut-off of >1.84×10^3 mm^2/s: R detected with a sensitivity of 70.6%, specificity of 80%, PPV of 80%, NPV of 70.6% and accuracy of 75%
									• ΔADC cut-off of 13.6% increase: R detected with a sensitivity of 88.2%, specificity of 86.7%, PPV of 88.2%, NPV of 86.7% and accuracy of 87.5%
Cheng *et al.* (23)	EC, gastric and GEJ cancer	236 (7 studies)	AC; SCC	CxT or CRT	• Baseline • Post NT	Pathological assessment in 4/7 studies	1.5 T MRI (6/7 studies, one not specified): DWI with variable b value from 0 to 1,000 s/mm^2	ADC values measured from 3D data in 3/7 studies, from 2D data in 2/7 and not specified in 2/7	• ΔADC: pooled sensitivity, specificity, DOR and AUC of 93% (95% CI, 77–98%), 85% (95% CI, 72–93%), 78 (95% CI, 15–401) and 0.91 (95% CI, 0.89–0.94) • Post-ADC: pooled sensitivity, specificity, DOR and AUC of 75% (95% CI, 62–84%), 90% (95% CI, 67–97%), 26 (95% CI, 6–110) and 0.85 (95% CI, 0.82–0.88)

Table 2 *(continued)*

Table 2 *(continued)*

Study	Localization	No. patients	Histology	Neoadjuvant therapy	Timing of scans	Pathological assessment	MRI modality	MRI parameters	Results
Weber *et al.* (24)	GEJ cancer (Siewert I-II)	15	AC	CxT (14 days), followed by CxT or CRT based on metabolic PET response (cut-off of SUV decrease of ≥35%)	MRI and FDG-PET/CT • Baseline • Post NT (after 14 days)	Becker score (R: grade Ia-Ib-II)	1.5 T MRI with respiratory gated DWI sequences (b value 50-400-800 s/mm²)	Mean of ADC values from 4 manual ROI (at least 80 pixels) avoiding necrotic areas	• Concordance of ADC increase and PET response observed in 73.3% of all patients • The ADC at first MRI and the tumor SUV at first PET/CT were not different in PET- R (SUV decrease of ≥35%) and NR; increase in ADC was significantly higher in PET-R (26.8%±22.2%) than in PET NR (6.5%±15.8%, P=0.0298) • ADC increase yielded a sensitivity, specificity, PPV and NPV respectively of 100%, 50%, 75% and 100% (cut-off) • GEJ with histological response had higher initial ADC values but not significant differences of ADC increase, initial SUV and SUV decrease • Non statistically significant differences in initial ADC and complete response (grade 1a)
Maffazzioli EC *et al.* (25)		158 (7 studies)	AC;SCC	CxT or CRT	• Baseline (6/7)	Mandard score in 5/7 studies (2/7 not specified):	• 4/7 studies 1,5 T MRI	ADC values measured from 3D data in 4/7 studies, from 2D data in 1/7 and not specified in 2/7 studies	• On pooled evaluation, baseline ADC was not significantly associated with pathological response (MD 0.11, 95% CI, 0.21–0.42; I^2=85%; P<0.01)
					• Interim evaluation (4/7)	• complete response (pCR, TRG1)	• 1/7 studies 3 T MRI	• PreNT ADC	• Two studies evaluated the differences in baseline ADC in pCR versus non pCR patients; in this subgroup analysis baseline ADC was significantly lower in pCR than non pCR patients
					• Post NT (7/7)	• good response (GR, TRG1-2)	• 2/7 studies not specified	• ΔADC from baseline to interim evaluation	• On pooled evaluation, a relatively increase in ADC at the interim evaluation of 21.06% was observed among responders (MD 21.06%; 95% CI, 13.04–29.09; I^2=49%; P=0.12). A similar increase was identified in pCR versus non pCR subgroups
							• DWI (b value 0-200-800 in 3/7 studies; 0-600 and 0-700 in 2/7 studies, 2/7 not specified)	• ΔADC from baseline to postNT evaluation	• On pooled evaluation, a relatively increase in ADC at the post NT evaluation was observed among responders (MD 22.49% 95% CI, 9.98–35.05; I^2=0%; P=0.46)

Table 2 *(continued)*

Table 2 *(continued)*

Study	Localization	No. patients	Histology	Neoadjuvant therapy	Timing of scans	Pathological assessment	MRI modality	MRI parameters	Results
Borggreve *et al.* (26)	EC	69	57 AC; 11 SCC; 1 Undifferentiated large cells carcinoma	CRT	MRI and FDG-PET/CT: • Baseline	Histological evaluation according to (30): TRG1:no residual cells; TRG2: 1–10% residual cells; TRG3 10–50% residual cells; TRG 4 >50% residual cells; pCR = TRG1 GR = TRG1-2	MRI with DWI (b value 0-200-800 s/mm²)	ADC: • mean ADC value	• Patients with SC had a significantly higher probability of pCR and GR than AC patients • The ΔADC between baseline and interim evaluation was associated with pCR (median, IQR: 28% [15%, 39%] for pCR versus 11% [4%, 17%] for non pCR, P=0.008), while ΔADC between baseline and post CRT evaluation were not statistically different. Same characteristics were found for R versus non-complete R
					• Interim evaluation (median of 13 days after initiation of CRT)			• ΔADC between baseline and interim evaluation	• Complementary role of FDG-PET/TC and DWI MRI for pCR prediction: ROC analysis showed that ΔADC between baseline and interim evaluation combined with ΔSUV between baseline and interim evaluation and histology have a superior bootstrapped c-statistic in comparison with their individual value and histology (0.83; 95% CI, 0.74–0.94), with the lowest AIC
					• Post NT			• ΔADC between baseline and post CRT evaluation	• No imaging parameters nor histology was associated to OS and DFS
Giganti *et al.* (27)	EC and GEJ cancer (Siewert I)	23; 9/23 CRT; 14/23 direct surgery	AC (9/23; 3/9CRT) SCC (14/23; 6/9 CRT)	CRT	• Baseline • Post CRT	Histological evaluation according to 7th TNM edition (31)	1.5 T MRI with DWI sequences (b value 0–600 s/mm²)	ADC (3D evaluation avoiding necrotic areas)	• Baseline ADC ≤1.4×10^{-3} mm²/s predicts negative prognosis in total population (P=0.016) and surgical group (P<0.001)
Heethuis *et al.* (28)	EC and GEJ cancer (EC34; GEJ 11)	45	38 AC; 5 SCC; 2 ASC	CRT	• Baseline	Mandard score	1.5 T MRI:	ADC and area under the concentration time curve (AUC):	• DW-MRI P75 ΔADC between post-NT and pre-NT was most predictive for GR (c-index =0.75)
					• Interim evaluation (weeks 2–3)	• pCR = TRG 1	• free breathing DWI sequences (b value 0-200-800 s/mm²)	• Mean	• DCE-MRI P90 ΔAUC between interim and pre-NT was most predictive for pCR (c-index =0,79); relative increase in tumor AUC of 10.6%±17.6% for partial R versus 45.2%±41.5% for partialNR
					• Post NT (3–9 weeks after CRT)	• GR = TRG 1-2	• DCE sequences	• Median • Several percentiles (P75/P90) • Δ between time points	• Complementary value of DWI an DCE for pCR prediction (c-index =0.89) by multivariable logistic regression analysis

CxT, chemotherapy; CRT, chemoradiotherapy; R, responders; NR, non-responders; ADC, apparent diffusion coefficient; DWI, diffusion weighted imaging; DCE, dynamic contrast enhanced; NT, neoadjuvant therapy; AC, adenocarcinoma; SCC, squamous cell carcinoma; ASC, adenosquamous carcinoma; V, volume; pCR, complete pathologic response.

mNR may provide surrogate information on phenotype of metastatic cancer clones beyond the mere presence of nodal metastases, and therefore its use might be suggested in order to better stratify patients and provide personalize treatments, including adjuvant therapy.

In *Table 3* the selected studies assessing the role of PET in neoadjuvant treatment response in GEJ cancer are reported.

The recent development of fully hybrid PET/MRI devices would represent the next step in hybrid imaging by combining the functional and metabolic characteristics of PET with the unique anatomical and functional information of MRI.

An interesting study by Belmouhand *et al.* (42) evaluated the feasibility of an early response assessment (3 weeks) to predict resectability using a hybrid 18F-FDG PET/MRI in patients treated with nCxT (n=22). Imaging identified 17 tumors as resectable and 5 as non resectable with a sensitivity and specificity of 94% and 80%, respectively for PET and MRI. Histopathology and RECIST were not correlated to resectability. This suggests that a multimodality imaging approach combining PET and MRI might provide complementary value for predicting pathologic response.

Radiomics

Radiomics is a novel tool consisting in extraction of quantitative data from medical images in order to develop predictive models relating imaging features to clinical outcomes. Only few studies incorporating radiomics in evaluation of treatment response in GEJ neoplasms exist, however early evidence suggests that imaging heterogeneity parameters could be prognostic.

In a cohort of 36 patients with contrast enhanced CT before and after nCRT, Yip *et al.* (43) reported that post treatment texture parameters are associated with OS; specifically, post treatment medium entropy of less than 7.356, coarse entropy of less than 7.116 and median uniformity of 0.007 or greater were associated with improved median OS, 33.2 *vs.* 11.7 months (P=0.0002). Furthermore, CT tumor heterogeneity decreases following nCRT in those patients with good response. The study also found that survival models which evaluated baseline (pre-treatment) texture parameters (entropy, uniformity) and maximal wall thickness perform better than maximal wall thickness alone in assessing survival.

Hou *et al.* (44) also found that CT based radiomic features can be used as imaging biomarkers to predict response to nCRT in an Asian population cohort with esophageal carcinoma.

Giganti *et al.* (45) studied pre-treatment first order energy, entropy, and skewness and found that they were significantly associated with a tumor aggressiveness and negative prognosis in 56 patients, supporting the claim that tumors with greater heterogeneity (e.g., higher entropy) are related to a worse outcome.

Table 4 tabulates the studies in which radiomic analysis was used to assess neoadjuvant treatment response in GEJ cancer.

Discussion

Current state of the art response assessment following neoadjuvant therapy in GEJ adenocarcinoma is suboptimal.

The few published studies specifically exploring the role of CT in assessing tumour response after nCRT in patients with GEJ adenocarcinoma have been inconclusive: changes in CT tumour dimension or volume do not represent a sensitive imaging biomarker in response evaluation. Furthermore, due to poor contrast resolution issue, CT is unable to adequately help differentiate between T1, T2 and T3 disease, compromising a precise downstaging assessment with low sensitivity and specificity (33–55% and 50–71%, respectively) (14).

Solutions to such issues could come from perfusion techniques: following neoadjuvant chemotherapy, normalization of tumor chaotic vasculature is hypothesized to occur, and it may reduce the pathological leakiness of the vessels and therefore decrease the extravasation of contrast agent from the intravascular compartment into the extracellular space. However, radiation could induce the release of proangiogenic factors and stimulate angiogenesis, thus impairing an optimal perfusion evaluation (14,15).

18F-FDG PET/CT has shown the most potential in this setting, since it can reliably discriminate early on between responder and non-responder status, thus providing information to choose the proper treatment strategy (35,37). Additionally, 18F-FDG PET/CT has been proven to adequately identify those patients with GEJ adenocarcinoma with worse prognosis after neoadjuvant chemotherapy completion (35). On the other hand, literature does indicate a limited value of 18F-FDG PET/CT in predicting overall pathological response (33). Furthermore, its accuracy could be affected by post treatment inflammation.

Potentially, a single imaging modality able to provide

Table 3 Studies that assessed the role of PET in neoadjuvant treatment response in GEJ cancer

Study	N. Pts	Histology	Neoadjuvant therapy	Timing of scans	Pathological assessment	PET parameters assessed	Results
Early response							
Zum Büschenfelde *et al.* (35)	56	AC	CxT	Baseline and 14 days after starting CxT	Histopathologic R (≤10% residual tumor) histopathologic NR (≥10% residual tumor)	Metabolic responders: mean SUV of 35% or more	18F-FDG PET as possible tool for guiding treatment algorithm and providing changes in treatment strategy early in the course of chemotherapy
Harustiak *et al.* (36)	126	AC	CxT	Baseline and after a median of 16 days after the start of chemotherapy (range, 12–22)	As per Mandard criteria	Variation of peak SUL and TLG of the primary tumor between PET1 and PET2: ΔSUL and ΔTLG	• No association between median ΔSUL or median ΔTLG and histopathological response • ΔTLG, but not ΔSUL, was associated with the histopathological response in a post hoc analysis of 47 pts with PET2 performed 16 days or less after the start of chemotherapy ΔTLG was 66 per cent or more
Schneider *et al.* (37)	30 (8 Gastric; 22 GEJ)	AC	CxT	Baseline and 14 days after starting CxT		Metabolic responders: decrease in SUV ≥35%	• 18F-FDG PET/CT reliably detect non-responders, thus allowing the identification of pts requiring an immediate change of therapy strategy (sens: 90.9%; spec: 47.3%; positive predictive value :50%; negative predictive value: 90%; accuracy: 63.3%)
Late response							
Kauppi *et al.* (32)	66	AC	CxT	Baseline and at the end of treatment (median time from last T and PET: 15 days)	According to Schneider *et al.* (40)	SUV Δ% [(SUV1-SUV2)/SUV1]x100	• Change in baseline SUV >67% optimally predict histopathological response (sens 79%; spec: 75%) • Change in baseline SUV >67% is associated with improved overall survival (HR 0.249, P=0.027) anddisease-free survival (HR 0.383, P=0.040)
Hernandez *et al.* (33)	192 (120 GEJ; 72 gastric)	AC	CxT or CXT and CRT	Baseline and at the end of treatment	–	SUVmax percentage change	• Significant correlation between SUVmax response and histologic response in patients with GEJ (rho =0.19, P=0.04) and gastric cancer (rho =0.44, P<0.0001) • SUVmax response failed to demonstrate a relationship with DSS in multivariable models containing conventional pathologic variables
Gabrielson *et al.* (34)	51	AC	CxT or CXT and CRT	Baseline and at the end of treatment Mean time between end of neoadjuvant therapy and follow-up PET/CT was similar in responders (15.7±9.2 days) and non-responders (17.9±24.9 days)	TRG grading describing the ratio of tumor cells to fibrotic cells, as suggested by Chirieac *et al.* (41)	SUR variation between baseline scan and post-treatment scan	• Significant SUR reduction in the primary tumor in histological responders compared to non-responders • Changes in SUR were significantly greater in responders following chemoradiotherapy, but not following chemotherapy alone • No difference in SUR in patients with complete histological response compared to pts with subtotal response

CxT, chemotherapy; CRT, chemoradiotherapy; AC, adenocarcinoma; GEJ, gastroesophageal junction; R, responders; NR, non responders; SUV, Standardized uptake volume; SUR, standardized uptake ratio (ratio between SUVmax of the tumor and SUVmean of a 1-cm^3 VOI placed within the mediastinal blood pool); TLG, total lesion glycolysis; SUL, standardized uptake value normalized to lean body mass.

Table 4 Studies that assessed the role of Radiomics in neoadjuvant treatment response in GEJ cancer

Study	Localization	N. patients	Histology	Neoadjuvant therapy	Timing of scans	Response assessment	CT parameters	Results
Yip *et al.* (43)	Esophageal cancer	36	26 SCC; 9 AC	Definitive CRT	• Baseline	RECIST criteria (46)	Wall thickness; texture analysis:	• Post CRT entropy <7,356, coarse entropy <7,116 and median uniformity ≥0.007 were associated with improved OS (P<0.01)
					• Post NT (median 65 days)		• entropy	• None of the baseline or changes in texture parameters after CRT nor morphological response assessment was associated with OS
							• uniformity • mean grey level intensity • kurtosis • SD of the histogram • skewness	• Survival models that combine pre-treatment entropy and uniformity with maximal wall thickness assessment, respectively, performed better than morphological assessment alone [AUC of 0.767 *vs.* 0.87 (P=0.00005) and 0.802 *vs.* 0.487 (P=0.0003)]
Giganti *et al.* (45)	Gastric and GEJ (Siewert II-III) cancer: • 2 Siewert II • 7 Siewert III • 47 Stomach	56	37 AC; 19 Signet-ring cell	None	• Baseline	Texture parameters and OS	107 radiomic features: • fist-order texture analysis • second-order texture analysis • shape and size features	• Kaplan-Meier curves were significantly different for 58/107 features and, after adjustment, for 50/107 texture parameters • Energy, entropy [no filter], entropy [filter 1,5], maximum HU value and skewness were associated to a negative prognosis in a multivariate model, according to different thresholds • Specifically, energy (2a), entropy [filter 1.5], maximum HU value, skewness, mean absolute deviation and root mean square were also predictors of OS at univariate analysis

CRT, chemoradiotherapy; AC, adenocarcinoma; HU, Hounsfield Unit; OS, overall survival; AUC, area under curve.

optimal soft tissue delineation together with functional information regarding tumour cellular proliferation, angiogenesis and microenvironment biology may be the best predictive and prognostic imaging tool. Early evidence suggests that MR, which provides a multiparametric, multiplanar assessment of the tumour burden with optimal soft tissue characterization (9) in association with an accurate depiction of functional modifications occurring early during neoadjuvant treatment, could play a major role in clinical practice. Specifically, recent literature highlights the role of DWI and DCE MRI, both providing intriguing insights into the biological environment of the tumour and on changes which occur therein during treatment.

Of note, the combination of PET and MRI, in particular when available as a full hybrid modality, could represent an optimal tool for evaluating GEJ treatment response after neoadjuvant treatment, since it might be able to both provide anatomical depiction as well as to quantify functional and metabolic information.

In this setting, imaging heterogeneity analysis will certainly represent an essential part of the overall treatment response assessment, even though further studies are needed.

In conclusion, imaging biomarkers can yield important information on tumour characterization and treatment response. However, overall prognosis of responders remains poor, suggesting underlying differences in tumour biology. Currently, data supports imaging biomarkers in detecting non-responders, which should be directly addressed to surgery without continuing neoadjuvant treatment.

A multimodal algorithm based on CT tissue density measures (dimensional evaluation), multiparametric MRI

which can yield quantitative data, in particular ADC, 18-FDG PET/CT and FDG PET/MRI using SUV and metabolic tumor volume with information on aggressiveness derived from radiomics, could aid in correctly evaluating and potential standardizing through a validation evaluation of treatment response.

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Footnote

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