Opportunities in Cancer Imaging: a Review of Oesophageal, Gastric and Colorectal Malignancies

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Abstract

The incidence of gastrointestinal (GI) malignancy is increasing worldwide. In particular, there is a concerning rise in incidence of GI cancer in younger adults. Direct endoscopic visualisation of luminal tumour sites requires invasive procedures, which are associated with certain risks, but remain necessary because of limitations in current imaging techniques and the continuing need to obtain tissue for diagnosis and genetic analysis. However, management of GI cancer is increasingly reliant on non-invasive, radiological imaging to diagnose, stage and treat these malignancies. Oesophageal, gastric and colorectal malignancies require specialist investigation and treatment due to the complex nature of the anatomy, biology and subsequent treatment strategies. As cancer imaging techniques develop, many opportunities to improve tumour detection, diagnostic accuracy and treatment monitoring present themselves. This review article aims to report current imaging practice, advances in various radiological modalities in relation to GI luminal tumour sites and describes opportunities for GI radiologists to improve patient outcomes

Introduction

Non-invasive radiological imaging is critical in the management of patients with gastrointestinal (GI) malignancies. The incidence of GI luminal cancers is increasing, particularly in younger adults[1]. There have been improvements in survival rates of colorectal cancer (5-year overall survival 60%) resulting from national screening programmes and more aggressive treatments in advanced disease, however the prognosis of oesophageal and gastric cancer remains poor (5-year overall survival 15% and 20%, respectively)[2].

Advances in cancer imaging techniques present opportunities to improve patient outcomes in various cancer sites. Optimisation of cancer detection, staging accuracy and treatment monitoring by enhanced radiological methods have the potential to improve patient selection for radical curative therapy, ultimately improving survival rates and quality of life. Patient selection for surgical resection is particularly pertinent in GI luminal malignancies because the respective operations carry significant morbidity and mortality rates due to their highly invasive nature. The reach of surgical and oncological treatments is expanding into areas including oligometastatic disease, which in colorectal cancer, are now considered amenable to surgical resection or stereotactic ablative radiotherapy (SABR)[3]. Advances in cancer imaging are likely to optimise patient management even further.

Contrast-enhanced computed tomography (CT) is the main radiological investigation in all luminal tumour sites for diagnosis, staging and monitoring response to treatment. Magnetic resonance imaging (MRI) is performed routinely for local staging of rectal cancer[4] and assessment of hepatic metastases in colorectal cancer. Positron emission tomography combined with CT (PET-CT) is used to stage patients with potentially curable oesophageal cancer and improves the sensitivity of detecting colorectal cancer recurrence[5]. MRI is used less frequently in upper GI malignancies, predominately as an additional investigation in cases with equivocal metastases on CT and PET-CT.

Newer cancer imaging techniques have been investigated in GI luminal malignancies and include new technologies including dual-energy CT and whole-body MRI (WB-MRI), quantitative techniques including perfusion CT and diffusion weighted imaging (DWI) and advanced computing analytics such as radiomic and artificial intelligence (AI).

This review article examines opportunities to develop and implement advances in radiological imaging in oesophageal, gastric and colorectal cancer.

Oesophageal Cancer

Diagnosis and Staging

Contrast-enhanced CT is used worldwide as the initial radiological staging investigation after histological confirmation of oesophageal cancer, usually after upper GI endoscopy and biopsy[6]. Staging CT is used to detect distant metastatic disease that precludes radical treatment. PET-CT is performed after CT in patients with potentially curable disease. The main advantage of PET-CT over CT is the greater sensitivity for distant metastases (52% vs 71%)[7], which prevents major surgery in those whom are unlikely to gain any positive benefit[8]. (Fig. 1) PET-CT up-stages patients with metastatic disease in up to 40% of cases[9], which subsequently reduces disease recurrence and improves survival rates after oesophagectomy[10].

Staging CT also provides an initial assessment of potential resectability, with sensitivity and specificity of 100% and 80% in one study[11], and is considered reliable for assessing advanced clinical T-stage. However, the diagnostic accuracy of CT falls dramatically in early-stage tumours. There is limited evidence that perfusion CT may enhance the sensitivity of diagnosing stage one tumours[12]. PET-CT should be avoided in high-grade dysplasia and T1 adenocarcinoma because

the diagnostic accuracy of staging metastatic disease is poor, particularly for distant metastases, where false positive results occur[13]. (Table 1)

Endoscopic ultrasound (EUS) has traditionally been considered the gold-standard investigation for loco-regional staging[7]. EUS provides good contrast resolution and differentiating individual layers of the oesophageal wall enables accurate T-staging[14]. EUS has good accuracy for detecting and staging early tumours. A meta-analysis of 19 studies showed EUS has a good sensitivity and specificity in staging T1a (0.85/0.87) and T1b (0.86/0.86) superficial esophageal cancer[15]. It is important to differentiate T1a from T1b tumours because the incidence of lymph node metastases rises to 5% in T1b tumours.[16]. As such, T1a tumours tend to be treated with endoscopic resection, whereas patients with T1b tumours undergo oesophagectomy[17], although more evidence is required to optimise treatment in these groups. EUS also provides the opportunity for fine needle aspiration (FNA) of suspicious lymph nodes which increases the diagnostic accuracy of metastases from 74% to 87%[18]. However, access to EUS services are variable and EUS is limited by non-traversable stenotic tumours, with passage rates being variable amongst operators[19].

MRI is a potential alternative for loco-regional staging (Fig. 2), especially in patients with a non-traversable tumour. MRI has been investigated for oesophageal cancer staging using high-resolution T2 sequences with cardiac and respiratory gating[20,21]. Accurate T- and N-staging of up to 100% has been demonstrated in ex-vivo feasibility studies with 4.7 Tesla (T)[22] and 7T[23] scanners. However, translation into clinical practice has been hampered by the limitations of MRI. (Table 1) Movement artefact from adjacent cardiac motion and diaphragmatic contractions degrade image quality. Accuracy of in-vivo staging has benefitted from echocardiogram (ECG) gating and high resolution endoluminal[24] and surface coils[21]. The latter study showed 1.5T MRI had comparable accuracy with EUS in differentiating T2 from T3 disease, but over-staged T1

tumours. Eighty-one percent of patients (28/37) were correctly T-staged when compared to histopathological stage. Under-staging and over-staging were demonstrated in 16.2% (n=6) and 8.1% (n=3), respectively.

The addition of diffusion weighted imaging (DWI) to MRI protocols has potential to improve accuracy in preoperative staging and measuring tumour length, which may surpass that of CT. A recent study including 78 patients found an overall accuracy of 63.2%, with a highest accuracy (83%) for T1 tumour staging, but general under-staged T3 tumours (42% accuracy)[25]. A limitation of DWI common to all cross-sectional modalities is the differentiation of peri-tumoural oedema from the primary tumour, which can hinder detection of adjacent lymph nodes and introduces error when measuring the length of disease for treatment planning.

The TNM classification defines regional lymph nodes as those draining the oesophagus, irrespective of the site of the primary tumour[26]. Coeliac axis and para-oesophageal nodes in the neck are included, but not supra-clavicular lymph nodes. Extensive data describing the diagnostic accuracy of lymph node staging exist. In general, all staging investigations tend to 'under-stage' lymph node metastases[27]. (Table 1) One meta-analysis found the sensitivity of CT, EUS and PET-CT for the detection of regional lymph node metastases was 50%, 80% and 57%, respectively[7]. The specificity was 83%, 70% and 85%, respectively. Another meta-analysis of PET-CT on nodal disease in SCC showed a sensitivity and specificity of 66 and 96% per node (65% and 81% per patient[28]). These figures show that EUS is more sensitive than CT and PET-CT, and EUS is less likely to under-stage disease.

A reason for suboptimal sensitivity is the size of nodal metastases. In patients radiologically staged cN0, 82% of lymph node metastases measured less than 6 mm and 44% less than 2 mm (classed as micro-metastases), which cannot be visualised on current imaging modalities. This

finding resulted in reduced sensitivity of CT, EUS and PET-CT (39.7%, 42.6% and 35.3%, respectively)[27].

Overall, the diagnostic accuracy of radiological staging must improve to optimise patient selection and treatment planning[29]. Advanced cancer imaging techniques should be developed to achieve this.

Treatment Response

CT

CT is also traditionally used to monitor treatment response after completion of neoadjuvant therapy prior to oesophagectomy. However, CT is insensitive for detecting residual disease after neoadjuvant therapy[30]. New techniques, such as dual energy CT[31], perfusion CT[32] and texture analysis[33] have shown promise in identifying responders to treatment and provide opportunities to personalise neo-adjuvant therapy. (Table 1)

Oesophageal blood flow[34] and mean transit time[35] measured by perfusion CT have predicted response to chemoradiotherapy and were associated with overall survival in advanced squamous cell carcinoma (SCC)[34], but only in small, single-centre studies. One such study of 32 patients showed a reduction of blood flow by 15% on perfusion CT to be associated with response to chemoradiotherapy at 2-3 weeks and overall survival[36].

Furthermore, CT perfusion parameters have been associated with pathological response. In a single-centre study of 40 patients, post-treatment blood flow of less than 30 mL min^{-1} $100g^{-1}$ corresponded with a complete pathological response[37]. Perfusion CT may identify patients likely to have a good response to their neoadjuvant treatment, but further research is required before clinical implementation. Similarly, in a single-centre study of 45 patients, normalised iodine

concentrations measured by dual energy CT (receiving 70 mL of 300 mg / mL iodinated contrast) identified non-responders after receiving chemoradiotherapy[31]. Early identification of non-responders is important, because the treatments are associated with significant side-effects and morbidity.

MRI

Quantitative analysis of DWI images have also shown potential to predict response and guide treatment decisions. MRI is an attractive opportunity for predicting and monitoring response to treatment because it is non-ionising, therefore multiple examinations can be performed during treatment[38]. Apparent diffusion coefficient (ADC) values have demonstrated an inverse association with tumour regression grade. In a study of 32 patients, ADC values showed significantly differed between responders and non-responders. Responders showed lower baseline ADC values (1.32 vs 1.63×10^{-3} mm^2/s; p=0.002) and higher post neoadjuvant therapy (2.22 vs 1.51×10^{-3} mm^2/s; p=0.001) than non-responders[39]. Again, these positive studies have been conducted with small sample sizes, in single centres.

Dynamic contrast enhanced (DCE) MRI has also been investigated for prediction of pathological treatment response. A single-centre study of 45 patients compared DCE-MRI with DWI and found they both provided complementary information in a multi-variable model. The c-index of DWI, DCE and combined for predicting treatment response was 0.75, 0.79 and 0.89, respectively[40].

The prospective, multi-centre PRIDE study is currently recruiting and will investigate PET-CT, DWI and DCE-MRI, measured pre-, during and post- neoadjuvant chemoradiotherapy before surgical resection to assess whether these techniques can better predict which oesophageal cancer patients have a better probability of a complete pathological response (pCR)[41]. The study

aims to recruit 200 patients. The primary aim is to develop and test a prediction model for pCR incorporating quantitative parameters derived from the PET-CT and MRI examinations.

PET-CT

PET-CT has an opportunity to play an important role in monitoring treatment response and re-staging oesophageal cancer. Whilst no single modality alone is currently accurate enough to identify complete responders to neoadjuvant therapies[42], PET-guided therapy is being investigated to guide pre-operative treatment of oesophageal cancer by identifying non-responders earlier in the treatment pathway and offering them alternative therapies[43,44]. (Fig. 3)

The MUNICON group investigated early PET-CT to predict response to neoadjuvant treatment in junctional adenocarcinoma. A reduction of 35% in maximum standardised uptake value (SUVmax) at 2 weeks was used to define metabolic responders, who continued to receive the planned neoadjuvant therapy, with non-responders progressing directly to surgery. In 104 patients who proceed to surgery, sensitivity and specificity for treatment response were 100% and 72% respectively, and metabolic responders had a better median event free survival (29.7 months) than non-responders (14.1 months)[45].

The preSANO study used PET-CT to identify residual disease in patients who underwent neoadjuvant chemoradiotherapy prior to surgery[30]. PET-CT missed 15% of non-responding tumours compared with endoscopy and biopsy (31%), bite-on-bite biopsies (10%), and EUS (28%). PET-CT also detected distant interval metastases in 18 of 190 patients (9%). This study highlights that a conservative “watch-and-wait” approach to oesophageal cancer is not feasible at present. (Table 1) Advances in cancer imaging may make this potential treatment strategy possible in future.

Traditionally, response assessment focusses on the primary tumour. Metabolic response of nodal metastases has also been assessed. Whilst nodal response usually matches that of the primary tumour, there is discordance in 5% of patients[46]. In addition, a metabolic nodal response (mNR) is prognostically significant, independent of established clinico-pathological markers and primary tumour response[47]. It is hypothesised that metabolic tumour response is a surrogate of pathological tumour response and mNR a surrogate of the recently described concept of pathological nodal response[48], although these concepts require further validation.

EUS

Unlike pre-treatment staging, EUS is of little clinical value in re-staging oesophageal cancer[49]. The accuracy of post neo-adjuvant EUS is relatively poor (59% for both T-stage and N-stage). EUS does not accurately detect down-staging of the tumour, even when a pCR is achieved because fibrosis can be indistinguishable from residual tumour[50]. Furthermore, chemotherapy can cause lymph node enlargement.

Quantitative Analysis

Researchers have utilised radiomics techniques to improve non-invasive assessment of oesophageal cancer. The concept of clonal evolution causing heterogeneity in solid tumours and their metastases has been confirmed with genomic analysis[51]. Hence, repeat biopsies during treatment may be required to change management according to the tumour evolution. This provides an opportunity for cancer imaging to become more precise.

Radiomics allow the high-throughput quantitative data extraction from medical images[52] in attempt to quantify intra-tumoural heterogeneity. (Fig. 4) Radiomics have also shown promise in predicting oesophageal cancer outcomes. Improvements in diagnostic staging, prediction of treatment response and survival have been shown when adding quantitative radiomics to traditional staging

methods[53]. A study of 400 patients showed incremental value in prognostic model performance when adding PET radiomics to radiological staging[54,55]. In a smaller study of 21 patients, textural uniformity of non-contrast enhanced CT images was associated with earlier tumour stage and better prognosis[33]. However, similar to other tumour sites, studies are often retrospective, single-centre and lack robust statistical methodology[56].

Gastric Cancer

Diagnosis and Staging

CT is the primary imaging modality used in gastric cancer. The main objective of CT staging in gastric cancer is to determine locally invasive disease and detect distant metastatic disease. (Fig. 5) However, CT is relatively inaccurate (60%) for differentiating early from advanced T-stage disease pre-operatively[57]. Similarly, the diagnostic accuracy of N-stage with CT in gastric cancer is relatively poor, as is CT in oesophageal cancer. The sensitivity of CT for regional lymph node metastases is 77% and the specificity is 63%[58]. (Table 2)

In contrast, EUS can discriminate between T1/2 and T3/4 disease, although a meta-analysis reported significant heterogeneity between published studies[59]. EUS is superior to CT for staging T1 tumours, but there is no advantage over CT in staging T2-4 disease[58]. Also, EUS has greater sensitivity for N-staging than CT in gastric cancer, but lower specificity[58]. The sensitivity and specificity of EUS for N-staging is 91% and 49%, respectively. Specificity for nodal disease increases with EUS-FNA, but few comparative studies explore the benefit of EUS-FNA in gastric cancer[60] because EUS is not routinely used. One study found EUS-FNA altered the management of 34/234 (15%) of patients[61]. Given the limited evidence, EUS is not routinely used in gastric cancer staging.

MRI has been investigated for local gastric cancer staging. After ingestion of water to distend the stomach, T2 spin-echo and gradient-echo sequences with breath-holding are often acquired. A meta-analysis of 11 studies including 439 patients showed MRI T-staging accuracy was 81%, however this was lowest in the T1 group[62]. When comparing T1/2 to T3/4 tumours, the pooled sensitivity and specificity was 93% and 91%, respectively. More recently, DWI has been investigated in gastric cancer. A subgroup analysis of papers showed that DWI increased the

specificity to 95%, whilst the sensitivity remained constant. Similar to the oesophagus, MRI is affected by movement artefact of the stomach, but advances in speed of MRI acquisition may allow accurate T-staging and identification of extra-mural vascular invasion, factors which are associated with a poor prognosis[63].

CT and MRI are similar in terms of N-staging accuracy[64]. Pooled estimates of sensitivity and specificity of MRI to differentiate node negative and positive disease are 86% and 67%[62]. In a single-centre study of 38 patients, MRI in combination with EUS was reported to increase the accuracy of diagnosing N2 disease compared to EUS alone (71.1% vs 68.4%)[65].

Common sites of distant metastases in gastric cancer include the liver and peritoneum. The latter prove challenging to detect using conventional CT because they are often small. (Table 2) One meta-analysis showed that although sensitivity of CT was 74%[66], peritoneal disease, present in around 10% of T2+ tumours, was undetectable by CT. Diagnostic laparoscopy is therefore advised for staging prior to radical curative surgery[67].

Non-invasive methods to detect peritoneal disease in gastric cancer have been investigated. Two systematic reviews[66,68] have shown that MRI is comparable to CT, but only a few comparative studies exist to date. In one study, investigating multiple primary tumour sites with 255 peritoneal tumour deposits, DWI improved the accuracy of peritoneal metastasis detection compared to conventional T1 and T2 MRI sequences[69]. Combined conventional MRI and DWI was the most sensitive imaging method to detect peritoneal disease, compared to DWI and conventional MRI alone (90% vs 71% and 73%, respectively).

PET/CT is also not used routinely in gastric cancer. In terms of lymph node staging, retrospective studies have shown that patients with PET positive lymph nodes had a mean recurrence free

survival of 36.5 months, compared to 60.4 months in patients without PET positive nodes[70]. However, the metabolic activity of the primary tumour was not associated with outcome. Background physiological uptake in the stomach impairs the differentiation of tumour, therefore accurate tumour segmentation is challenging.

PET-CT has also been investigated to improve distant metastatic staging accuracy in gastric cancer. Occult metastases that were undetected on CT were found in 4.7% of patients[71]. This is an important finding which prevents patients having major, life-changing surgery with little chance of positive benefit. The prospective, multi-centre PLASTIC trial will investigate PET-CT prior to staging laparoscopy in attempt to reduce the total number of unnecessary surgical procedures[72]. The trial aims to recruit at least 240 patients with locally advanced gastric cancer with primary outcome being the proportion of patients in whom the addition of PET-CT and staging laparoscopy changed treatment strategy.

Treatment Response

All imaging modalities are currently inaccurate for evaluating treatment response. (Table 2) CT is often performed prior to surgical resection in patients treated with peri-operative chemotherapy to ensure disease progression has not occurred in the interim. Like esophageal cancer, EUS is inaccurate at tumour staging post neoadjuvant treatment. Endosonographic features such as tumour thickness have been associated with recurrence, and may be useful as prognostic markers, but must be validated in larger studies[73].

Radiomics have also been investigated in gastric cancer. One small study (n=26) showed heterogenous texture features in patients with HER-2 positive gastric cancer were associated with better prognosis (five-fold increase in median survival) after receiving trastuzumab[74]. A large, multi-centre retrospective analysis in more than 1,500 patients used regression modelling to

328 determine a radiomic signature that, when combined with clinico-pathological factors, marginally
329 improved the discrimination (c-index) of the TNM staging model from 0.80 to 0.85 for disease-
330 free survival, and from 0.80 to 0.86 for overall survival[75].
331
332 These techniques show potential, but the methodology used is often yields false-positive results[56].
333 Rigorous statistical analysis must be used to enable clinical testing and adoption. Commonly,
334 studies with small samples sizes test too many variables in a model[76]. Furthermore, image
335 features are not standardised between scanners, and methodology is poorly reported, therefore
336 external validation studies often fail to replicate the original results[77].
337

Colorectal Cancer

Colorectal cancer (CRC) is the second most common malignancy in the UK and accounted for 10% of the total UK cancer deaths between 2015 and 2017[78]. CT is the primary imaging modality for the investigation, diagnosis and monitoring of colorectal cancer (CRC).

CT

Since the publication of the SIGGAR trials, CT colonography (CTC) has replaced barium enema for the investigation of suspected CRC[79,80]. The trials showed that the detection rate of large polyps and CRC was significantly higher for CTC than barium enema. Other advantages of CTC are that same-day colonoscopy can be performed for direct visualisation, with or without biopsy, if an abnormality is demonstrated on imaging.

Faecal immunochemical testing (FIT) provides an opportunity to streamline CTC services further, triaging those patients at higher risk of CRC for imaging more urgently[81]. FIT is more sensitive, cost effective and easier to use than its predecessor gFOBt[82]. The high negative predictive value reliably identifies those without CRC. Farrugia et al[83] found that 91% of patients with a normal CTC or colonoscopy were FIT negative meaning that those at low risk of CRC could be triaged safely.

Computer Aided Diagnosis (CAD) has advanced interpretation of CTC images. (Fig. 6) CAD can be used as a primary, secondary or concurrent reader[84]. Halligan et al[85] demonstrated that CAD as a secondary reader significantly increased sensitivity when detecting polyps 6 mm or larger and polyps 5 mm or smaller, and concurrent CAD had improved sensitivity when detecting polyps 5 mm or smaller. CAD as a second reader improves polyp detection rate in clinical practice[84,85].

Contrast-enhanced CT is currently used to evaluate the anatomical extent and distribution of CRC. As with oesophageal and gastric cancer, it is vital that radiological staging is accurate to guide treatment selection. This is especially important considering the recent FOxTROT trial demonstrated that neoadjuvant chemotherapy improved the rate of downstaging and incomplete resections compared to surgery and adjuvant therapy[86].

MRI is widely used for local staging of rectal cancer to guide use of neoadjuvant therapy by assessing circumferential resection margin involvement, for example. Traditionally, the TNM classification has been used to stage CRC, but recent evidence has suggested that the presence of tumour deposits and extra-mural vascular invasion (EMVI) on MRI may have greater prognostic significance in patients with rectal cancer[87].

Additional functional information may be obtained using advanced imaging techniques, but current evidence is limited. (Table 3) CT perfusion studies can provide additional information about the vascularity of the tumour, quantify regional blood flow, blood volume, and the rate of transfer of contrast agents from the intravascular to extravascular space. (Fig. 7) For example, tumoural blood flow, blood volume and vascular permeability are higher than normal colon. Typically, blood flow ranges between 50–200 mL min^{-1} 100 g^{-1} of tumour tissue versus 10–40 mL min^{-1} 100 g^{-1} of normal tissue[88].

Differences are also seen between tumour and inflammation. A study of 60 patients with diverticular disease, acute diverticulitis or cancer showed that higher blood flow was demonstrated in cancer compared to diverticulitis (80 mL min^{-1} 100 g^{-1} vs 52 mL min^{-1} 100 g^{-1}, respectively), but overlap in parameter values between these two conditions was evident[89].

Small, single-centre clinical studies have shown that patients with poorly perfused tumours have poorer survival. Hayano et al showed that in rectal cancer (n = 44)[90], patients with poorly perfused tumours (blood flow <40 mL min^{-1} 100 g^{-1}) were more likely to have a poorer overall survival.

Quantifying angiogenesis with CT perfusion may be useful to assess treatment response[91]. Relatively few published studies in CRC exist. Neo-adjuvant chemoradiotherapy has been shown to decrease blood flow by more than 40% in advanced rectal cancer[92,93]. This technique also has relevance for anti-angiogenic therapies, however evidence for their use is currently limited and they are not routinely used in UK CRC management.

There are limitations of CT perfusion that must be addressed prior to clinical adoption[91]. CT perfusion quantification is affected by movement artefact, such as motion from breathing, peristalsis and mobility of the mesentery. Motion-correction software, intravenous anti-cholinergics and breath holding are techniques that may improve image quality. In addition, there are many steps to acquiring CT perfusion images and the imaging protocols and processing methods are complex[91]. There is an element of operator-dependency. The operator needs to select the ROI in order to measure the perfusion parameters which can introduce bias. Standardisation of the technique would be beneficial in order to make the technique reproducible and comparable.

Goh et al are conducting a clinical trial (PROSPeCT) which evaluates whether using parameters from CT perfusion improves prediction of clinical outcomes in primary colorectal cancer[94]. The trial is primarily looking into the prediction of metastatic disease.

MRI

MRI is currently used in the primary staging of rectal cancer and as an additional investigation to detect liver metastases following equivocal contrast-enhanced CT.

Advances in high resolution MRI provides the opportunity to more accurately differentiate between T1 and T2 tumours, and thus offer local excision where appropriate. Balyasnikova et al[95] demonstrated that MRI was able to differentiate between partial and full submucosal invasion with 89% accuracy in patients with early rectal cancer (ERC). The MINSTREL[96] and PRESERVE clinical trials[97] aim to assess the performance of MRI in ERC and the effectiveness of a new MRI staging protocol in identifying patients with early rectal cancer, respectively. The outcomes of these trials would mean that MRI would be able to guide management more accurately, such as offering local excision rather than radical surgery.

Wu et al[98] performed a meta-analysis including 11 studies of 537 patients concerning the diagnostic performance of DW-MRI in patients with liver metastases. The results of the meta-analysis concluded that DW-MRI in combination with contrast-enhanced MRI (CE-MRI) had higher pooled sensitivity and specificity (97% and 91%) than DW-MRI alone (87% and 90%), but DW-MRI was still relatively accurate. Notably, the pooled specificity of DW-MRI was higher at 3T MRI than using 1.5T MRI (91% vs 81%).

A DW-MRI sequence is relatively fast (5-10 mins) and does not require contrast, thus presents a feasible option to concurrently assess for liver metastases at the time of CRC diagnosis. The SERENADE trial aims to evaluate whether DW-MRI of the liver at the time of CRC diagnosis can identify more liver metastases than conventional CT[99]. If successful, then CRC imaging pathways could become more streamlined, reducing time to treatment for each patient.

Taylor et al[100] recently reported the STREAMLINE-C trial comparing the diagnostic accuracy and efficiency of whole-body MRI (WB-MRI) staging with standard pathways for staging CRC. (Fig. 8) The trial found that WB-MRI had a similar accuracy and was more efficient (reduced number of tests, reduced time to complete staging and NHS costs) than standard pathways. (Table 3) Furthermore, patients prefer WB-MRI staging compared to standard pathways[101]. WB-MRI has the potential to augment standard staging pathways, with benefits including reduced radiation dose, increased efficiency, and reduced costs.

Treatment response and monitoring

MRI based tumour regression grade (mrTRG) is used to assess pre-operative treatment response of locally advanced rectal cancers[97,102,103]. (Fig. 9) mrTRG is based on the Mandard tumour regression grading system originally derived from resected oesophageal carcinoma specimens. The change in MRI signal is used as a surrogate marker of underlying fibrosis resulting from treatment[104]. Patel et al[105] demonstrated that patients with a good response using mrTRG had a 5-year overall survival of 72% compared to 27% in those with a poor response. Furthermore, the addition of DWI to standard MRI sequences improves the accuracy of predicting complete responders. In a multi-centre of 120 patients with locally advanced rectal cancer, Lambregts et al[106] found the sensitivity for predicting complete response was 0-40% for standard MRI sequences and 52-64% with added DWI. (Table 3) Specificity was high (89-98%) for both.

Clinical trials are currently investigating whether determination of treatment response on imaging is accurate and can sufficiently predict long-term outcomes. TRIGGER is a phase 2/3 clinical trial evaluating whether good and poor responders, determined by mrTRG, can be used to alter treatment decisions, such as selectively offering surgery or additional pre-operative treatment[97].

In particular, a watch-and-wait approach is being investigated in rectal cancer. Martens et al[107] found that organ preservation with a watch-and-wait approach in selected patients with a complete or near-complete response had a low colostomy rate and good long term functional outcome. Presently, there is ongoing debate about how to implement a watch-and-wait approach in clinical practice. For example, the time interval of MRI re-staging is contentious. It has been suggested that a longer interval of MRI re-staging may be beneficial[108,109]. Sloothaak et al[108] suggested that delaying surgery until the 15th or 16th week after the start of chemoradiotherapy resulted in the highest chance of pathological complete response. West et al[109] suggested that MRI restaging at week 14 compared to week 9 resulted in greater tumour down-staging and volume reduction. Current European Society of Gastrointestinal and Abdominal Radiology (ESGAR) guidance is to combine re-staging MRI with clinical examination (digital rectal examination and endoscopy) when considering "watchful waiting" organ preservation after chemoradiotherapy[110].

PET-CT

PET-CT is currently used in cases of CRC recurrence where surgical resection is being considered. (Fig. 10) PET-CT has a sensitivity of 94% and specificity of 77% for CRC recurrence in meta-analysis[5]. The future application of PET-CT may also include assessment of treatment response.

A meta-analysis including 34 studies and 1526 patients showed that PET-CT had a pooled sensitivity and specificity of 73% and 77% for predicting response to neo-adjuvant therapy in rectal cancer. Furthermore, diagnostic accuracy was better 1-2 weeks after beginning chemo-radiotherapy, with pooled sensitivity and specificity of 84% and 81%, respectively). These studies indicate that PET-CT may offer another opportunity to guide pre-operative treatment leading to

more individualised management, though it is not currently recommended to monitor treatment response at present.

Quantitative Imaging

Multi-parametric imaging has the potential to improve understanding of biological processes, phenotyping tumours and predicting treatment responses[111]. PET-CT in combination with perfusion CT has signalled further improvements in tumour grading[88,112]. It is hypothesised that a mismatch between perfusion and metabolism may indicate a more aggressive phenotype. A tumour with poor perfusion, but high metabolic activity, may reflect adaptation to intra-tumoral hypoxia, and may be more resistant to treatment[111].

Similar to upper GI cancers, several radiomics studies have been conducted in CRC. Huang et al[113] performed a supervised machine learning algorithm to create a radiomic nomogram which predicted pre-operative lymph node metastasis in CRC. The nomogram incorporated CT (portal venous phase) features and clinical risk factors. The nomogram stratified patients according to their risk of lymph node metastases. Studies have also integrated PET radiomics features with tumour biology[114]. Chen et al[115] demonstrated associations between genetic mutations (KRAS, TP53 and APC) in CRC with PET radiomics features.

Furthermore, radiomics features have been associated with the pre-treatment immune micro-environment within tumours. Sun et al[116] developed a radiomics biomarker using CT images and gene sequencing data in order to evaluate the immune phenotype of solid tumours. The study included a wide range of solid tumours, of which a minority were CRC. The radiomics biomarkers were able to identify a high or a low infiltration of CD8 cells, which was associated with treatment response to programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) immunotherapy. Further studies are expected to validate the initial findings from this study.

Conclusion

This review highlights the opportunities that exist in cancer imaging of oesophageal, gastric and colorectal malignancies. Advances in imaging techniques, hardware and software have created a wealth of tools that have shown promising early results improving diagnostic accuracy and patient outcomes. Further research must be conducted to test the clinical utility of these advances, and national trials must be completed between collaborating GI radiologists to ensure these techniques have a positive impact for patients.

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Figure Legends

Figure 1. A patient with a gastro-oesophageal junction adenocarcinoma who was being considered for neo-adjuvant therapy and surgical resection. A PET-CT was performed to look for distant metastatic disease undetected on CT. The PET-CT demonstrated an FDG-avid retroperitoneal lymph node metastasis below the level of the renal veins, thus upstaged the patient to M1 disease, precluding them from radical treatment.

Figure 2. Selected image from an axial T2 HASTE MRI sequence of a healthy volunteer demonstrating the layers of the normal oesophageal wall. The mucosa is low signal (white arrow), the submucosa is high signal (long black arrow) and the muscularis propria (short black arrow) is intermediate signal.

Figure 3. An example of pseudo-progression following neo-adjuvant chemoradiotherapy. This male patient was originally stage with a T3N0M0 gastro-oesophageal adenocarcinoma. After completion of neo-adjuvant chemotherapy, a re-staging PET-CT was performed which showed progressive metabolic disease. The pre-treatment metabolic tumour length was 4 cm and the SUVmax was 8.8. Following treatment, the metabolic tumour length was 8 cm and the SUVmax was 11.6. However, there was a good clinical response, and no distant metastases were demonstrated, therefore the increased metabolic activity was considered to be inflammation following radiotherapy and conformed to the gross tumour volume.

Figure 4. A schematic showing the basic radiomics pipeline, from acquisition and preparation of medical imaging, segmentation of regions of interest, feature extraction and clinical model development.

Figure 5. A selected CT image showing a locally advanced gastric antrum tumour (white arrowheads), with liver metastases (red circle) and peritoneal deposits (white arrow).

Figure 6. A patient with a 6 mm colonic polyp detected by computer aided diagnosis (CAD). Selected images of a) a multi-planar reconstruction CT and b) a three-dimensional endoluminal volume rendered reconstruction.

Figure 7. Selected images from a CT perfusion study showing a) blood flow, b) blood volume and c) permeability parameters in a heterogeneous rectal tumour. Courtesy of Professor Vicky Goh, Kings College London.

Figure 8. Coronal whole-body water only Dixon sequence showing a stenosing sigmoid tumour (short arrow) with liver metastasis (long arrow).

Figure 9. a) Angled high resolution axial T2 weighted image through the lower rectum shows a small tumour (arrow) which was treated with long course chemoradiation. b) Repeat MRI 4 months later shows a complete radiological response with a thin band of residual low signal fibrosis only (arrow).

Figure 10. This patient had a right hemicolectomy for an ascending colon adenocarcinoma 12 months prior. A contrast-enhanced CT showed a suspected single site of recurrence in the right iliac fossa. A PET-CT was requested which confirmed the right-sided recurrence (a). However, other sites of abdominal disease were also demonstrated (b), therefore non-operative management was pursued. Courtesy of Dr Patrick Fielding, Wales Research & Diagnostic Positron Emission Tomography Imaging Centre.

967 **Table Legends**

968 Table 1. Pitfalls in Oesophageal Cancer Imaging.

969 Table 2. Pitfalls in Gastric Cancer Imaging.

970 Table 3. Pitfalls in Colorectal Cancer Imaging.

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973 Table 1. Pitfalls in Oesophageal Cancer Imaging.
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Imaging Pitfall	Impact on Clinical Practice	Opportunities for Improvement
Poor detection of early-stage tumours with CT	Poor detection of early-stage tumours which limits the proportion of patients with early disease who can be treated radically, where the survival benefit is greatest.	1. Better collaboration between endoscopy and radiology services to allow rapid access to CT in select patients. 2. Alternatives modalities such as CT perfusion and MRI in select patients known to be high-risk for oesophageal cancer, such as those with extensive Barrett's oesophagus.
Suboptimal lymph node staging	Suboptimal selection of patients for specific treatments. If disease under-staged, then greater likelihood of recurrence after major surgical intervention and/or oncological therapy. If over-staged, then patients denied potentially beneficial treatment.	1. Improved understanding of tumour biology, genomics, underlying microenvironment and metastatic potential. 2. Greater understanding of peri-oesophageal lymphatic system. 3. Improved technology, such as high-resolution PET and MRI imaging, to

		allow greater differentiation of normal and malignant lymph nodes. 4. Standardised staging protocols to allow better patient selection for treatments.
Suboptimal distant metastatic staging	Although specificity is good, the sensitivity of CT and PET-CT has the potential to miss distant metastases.	1. Improved understanding of tumour biology and metastatic potential. 2. Better CT, PET and MRI imaging technology to allow higher contrast and spatial resolution to detect small distant metastases. This includes digital PET-CT, novel radioisotopes and whole-body MRI.
Limited prediction of treatment response and residual disease assessment a. Early b. Late	The majority of patients do not have a good pathological response to neoadjuvant therapies. a. Early treatment response assessment would allow those unlikely to benefit from neoadjuvant therapy to have alternative therapy or proceed directly to surgery. b. Accurate assessment of those whom have had a response or residual disease would identify patients for potentially new adjuvant treatments e.g. immunotherapies that are being developed.	1. Greater understanding of tumour biology and its relevance on imaging features of the primary tumour and metastases. 2. Serial imaging and biopsies to monitor clonal tumour evolution. 3. Quantitative imaging e.g. radiomics and deep learning approaches 4. Novel radioisotopes. 5. Multi-modal imaging strategy to optimise diagnostic accuracy.

Table 2. Pitfalls in Gastric Cancer Imaging.

Imaging Pitfall	Impact on Clinical Practice	Opportunities for Improvement
Suboptimal diagnostic accuracy of loco-regional staging	Suboptimal patient selection for surgery results in high rates of recurrence and influences subsequent quality of life.	1. Greater understanding of tumour biology and metastatic potential. 2. Better imaging technology including high-resolution MRI and digital PET to improve contrast and spatial resolution of serosa disease and small lymph node metastases.
Suboptimal diagnostic accuracy of distant metastatic disease	Suboptimal patient selection for surgery, oncological and/or palliative therapies. Greater rates of disease recurrence and impacts on overall survival.	Better imaging techniques to allow greater detection of small metastatic disease such as those in the peritoneum and liver.
Suboptimal assessment of treatment response	A growing number of peri-operative immunotherapies are available that have shown improvements in overall survival. Currently poor prediction of patients who will respond and poor identification of patients who have responded to treatments.	1. Better understanding of tumour biology, genomics and tumour microenvironment with serial biopsies. 2. Improved imaging to detect image features of treatment response using radiomics and deep-learning techniques.

981 Table 3. Pitfalls in Colorectal Cancer Imaging.
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Imaging Pitfall	Impact on Clinical Practice	Opportunities for Improvement
Suboptimal staging pathways	Fully optimised staging pathways would a. improve the diagnostic accuracy of radiological staging, b. reduce the time to treatment, c. optimise patient selection for treatments, and d. improve the cost-effectiveness of the colorectal cancer staging pathway.	1. Whole-body MRI has the potential to make staging pathways more efficient and cost-effective. 2. Greater emphasis on optimised staging according to tumour location e.g. right versus left colon tumours, tumour deposits and EMVI in rectal cancer.
Suboptimal treatment response prediction in colorectal cancer	Accurate prediction of treatment response would allow patient stratification for surgery and (neo)adjuvant therapy.	Novel imaging techniques such as CT perfusion studies, PET-CT and MRI may improve the assessment of treatment response allowing groups of patients to be selected for novel (neo)adjuvant therapies.
Suboptimal prediction of complete pathological response in rectal cancer	Accurate prediction of a complete pathological response would allow a safe watch-and-wait approach in patients with colorectal cancer. This would greatly reduce the morbidity associated with surgical resection.	Improved imaging techniques to accurately classify the MRI tumour regression grade, for example optimised diffusion weighted imaging.

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