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Colorectal cancer: imaging surveillance following resection of primary tumour

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Abstract

Most patients with colorectal cancer undergo treatment with curative intent and subsequently enter a surveillance programme. The primary aim of surveillance is to identify patients with disease relapse at a resectable stage. However, the identification of local recurrence and metachronous carcinoma are also important aspects of follow up. Patients under observation may be referred for imaging either because regular imaging forms part of the surveillance strategy, or because tumour relapse is suggested by the development of new symptoms or a rise in tumour markers. This paper reviews the use of new and existing imaging techniques during surveillance following resection of primary colorectal cancer. The use of imaging for this surveillance is an application of cancer imaging that is supported by evidence-based clinical guidelines. Computed tomography provides the mainstay modality on grounds of good overall diagnostic performance combined with high availability and low cost. Improvements in survival with more aggressive follow up and treatment are likely to demand more accurate imaging techniques in the future.

Keywords: *Colorectal cancer; computed tomography; magnetic resonance imaging; positron emission tomography; imaging biomarkers; clinical guidelines.*

Introduction

Colorectal cancer is the second most common malignancy in Western societies with approximately 145,000 new cases diagnosed in the US each year[1]. Most patients undergo resection of the primary tumour but up to 40% of these patients will relapse and die of their disease[2]. In 20–40% of patients with relapse, the liver is the sole site of metastases[3]. Approximately 75% of newly diagnosed patients undergo treatment with curative intent and subsequently enter a surveillance programme[4]. The primary aim of surveillance is to identify patients with disease relapse at a resectable stage, as liver metastasectomy can be associated with an improved 5-year survival of 33%[5]. The identification of local recurrence, which occurs in over 11% of colon cancers, and/or metachronous carcinoma (Fig. 1), with its annual incidence of 0.18%, are also important aspects of follow up[6,7]. Colorectal cancer patients under observation may be referred for imaging either because regular imaging forms part of the surveillance strategy, or because tumour relapse is suggested by the development of new symptoms or a rise in the serum carcinoembryonic antigen (CEA). The use of imaging for surveillance is supported by a meta-analysis which has shown that after primary resection the intensification of follow up by the inclusion of imaging is associated with reduced mortality (odds ratio = 0.66, 95% confidence limits 0.46–0.95)[8]. The American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) now recommend imaging follow-up of patients with colorectal cancer[9,10]. However the best strategy for surveillance remains debated with definitive trial data as yet unavailable[11].

Clinical review and CEA

ASCO recommends clinical follow up every 3–6 months for the first 3 years and then 6 monthly to at least 5 years.

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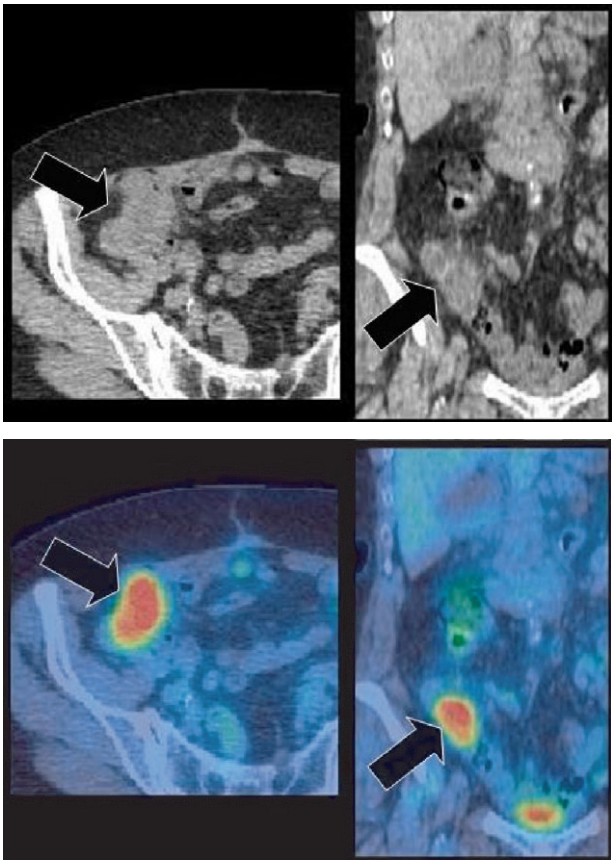

Figure 1 **Metachronous tumour (arrow) discovered on PET-CT performed for rising tumour marker.**

Patients with stage II or III disease have serum CEA every 3 months for at least 3 years, provided the patient is a candidate for surgery or systemic therapy[9]. The recommendations of the European Society for Medical Oncology are similar, i.e. CEA every 3–6 months for 3 years and every 6–12 months in years 4 and 5[10].

Ultrasound and chest radiography

ESMO recommend ultrasonography of the liver every 6 months for 3 years and after years 4 and 5 together with annual chest radiography[10]. However, the sensitivity of ultrasonography for the detection of hepatic metastases from cancers of the gastrointestinal tract is lower than that of computed tomography (CT)[12]. Furthermore, the ability of ultrasonography to detect extra-hepatic metastases and metachronous tumour is limited. Therefore despite this recommendation CT is probably favoured by most units.

Computed tomography

After primary therapy for patients at higher risk of recurrence, typically those with node-positive tumours, ASCO recommends annual computed tomography (CT) of the chest and abdomen for 3 years extended to include the pelvis in rectal cancer patients[9]. A recent systematic review of studies comparing the diagnostic performance of different imaging modalities for the detection of colorectal liver metastases found the sensitivity of non-helical CT on a per-patient basis to be 60.2% with helical CT achieving a sensitivity of 64.7%[13]. CT is the imaging modality of choice for the detection of lung metastases which compared with liver secondaries are less likely to be associated with a raised tumour marker but are as common and more readily resectable[9].

Local relapse in rectal carcinoma has significantly reduced since the introduction of total mesorectal excision (TME)[14]. The sensitivity for CT in this scenario is reported to be 82%[15]. However, specificity is as low as 50% reflecting the difficulty in distinguishing recurrent tumour from post-operative fibrosis. The use of a multidetector CT system with multi-planar reconstructions can improve diagnostic performance[8]. That said, patients with CT appearances suggesting recurrence often undergo fluorodeoxyglucose (FDG)-positron emission tomography (PET) to confirm the presence of active tumour if disease is not visualised on endoscopy (Fig. 2).

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has a higher sensitivity (75.8%) than CT for the detection of colorectal liver metastases which is further improved with the use of superparamagnetic iron oxide (SPIO)[13]. However, the higher cost of MRI and its limited value in detecting lung metastases precludes its use over CT for routine surveillance. It is therefore reserved for more accurate staging of the liver often when surgery or thermal ablation is being considered. Furthermore MRI is more sensitive than CT for the detection of pelvic recurrence where once again it may be useful in treatment planning particularly where the surgical resection plane requires definition (Fig. 3). However the use of MRI as part of routine follow-up has been questioned. In a study of 226 patients, MRI detected the same proportion of resectable tumours (4 of 6) as that diagnosed by conventional follow-up tests[16]. Although two additional cases of resectable tumour were found when MRI was used in addition to conventional tests, this benefit was considered to be outweighed by a large proportion (14%) of false-positive tests resulting in additional cost and patient anxiety.

Positron emission tomography-computed tomography

Positron emission tomography with fluorodeoxyglucose (FDG-PET) is significantly more sensitive (94.6%) than

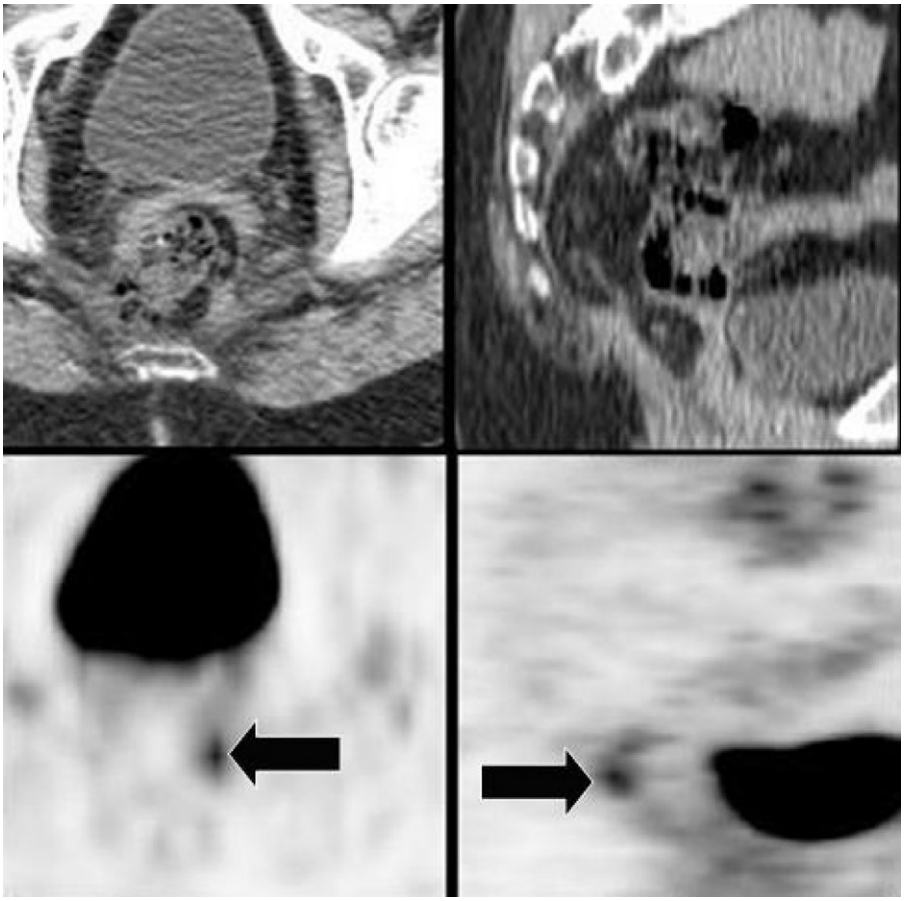

Figure 2 **Small recurrent rectal cancer (arrow) discovered on PET-CT in a patient presenting with persistent perineal pain.**

CT or unenhanced magnetic resonance imaging (MRI) for the detection of liver metastases on a per patient basis[13]. However, as for MRI, the high cost and lower availability of PET precludes the use of this modality for routine surveillance. The role of FDG-PET in the management of hepatic recurrence is to confirm operability through exclusion of otherwise unsuspected additional metastatic sites (Fig. 4). Comparative sensitivity values for extra-hepatic disease range from 58 to 74% for CT, vs. 90–100% for FDG-PET, whilst specificity values are similar for the two modalities[17]. Exclusion of extra-hepatic metastases may also be useful prior to aggressive local treatments for hepatic metastases such as radiofrequency ablation or intra-arterial microsphere-based radiotherapy.

FDG-PET is also of value in the investigation of patients with raised tumour markers and negative conventional imaging. The positive yield of FDG-PET in this situation ranges between 38 and 77%[17] and this role for PET has been shown to be cost-effective in many countries[17]. In some cases, a localised tumour deposit potentially amenable to surgery is found (Fig. 5). However, in a significant proportion of these patients, PET is found to have underestimated the extent of disease at surgery. This is likely to fall with the use of integrated PET-CT which is able to more reliably distinguish omental/peritoneal disease from physiological bowel uptake when compared with PET alone[18]. Occasional false positive diagnoses on PET are a further limitation, most commonly inflammatory conditions, amongst patients investigated for a rising CEA[17].

Colonoscopy

Although sometimes discovered as an incidental imaging finding, the detection of metachronous tumour is usually achieved with colonoscopy. ASCO recommends colonoscopy at 3 years post-primary resection and, if normal, every 5 years thereafter. More intense endoscopy is necessary for those at increased genetic risk[9]. CT colonography shows promise as an alternative to colonoscopy and could readily be combined with conventional CT or even PET-CT in a single examination[19]. A single study that evaluated CT colonography during surveillance

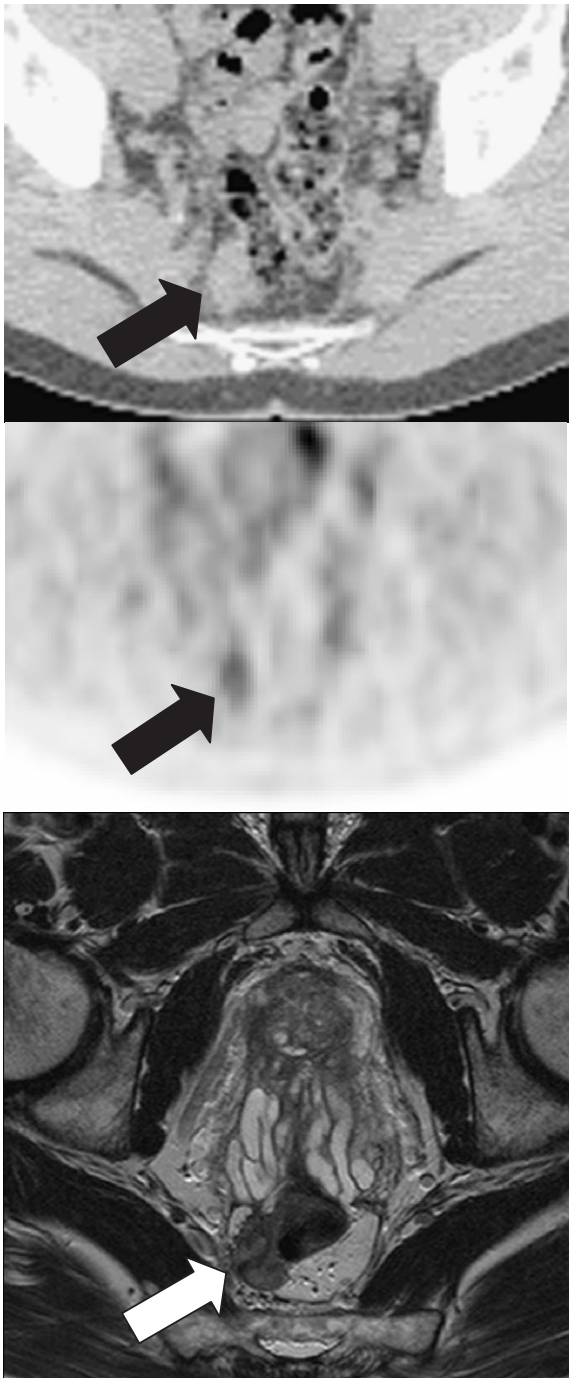

Figure 3 **A new soft tissue mass at the level of the anastomosis following abdomino-perineal resection for a rectal carcinoma. The lesion was not apparent at sigmoidoscopy. FDG-PET only revealed low to moderate grade uptake (black arrow). MRI was performed to plan local therapy (white arrow).**

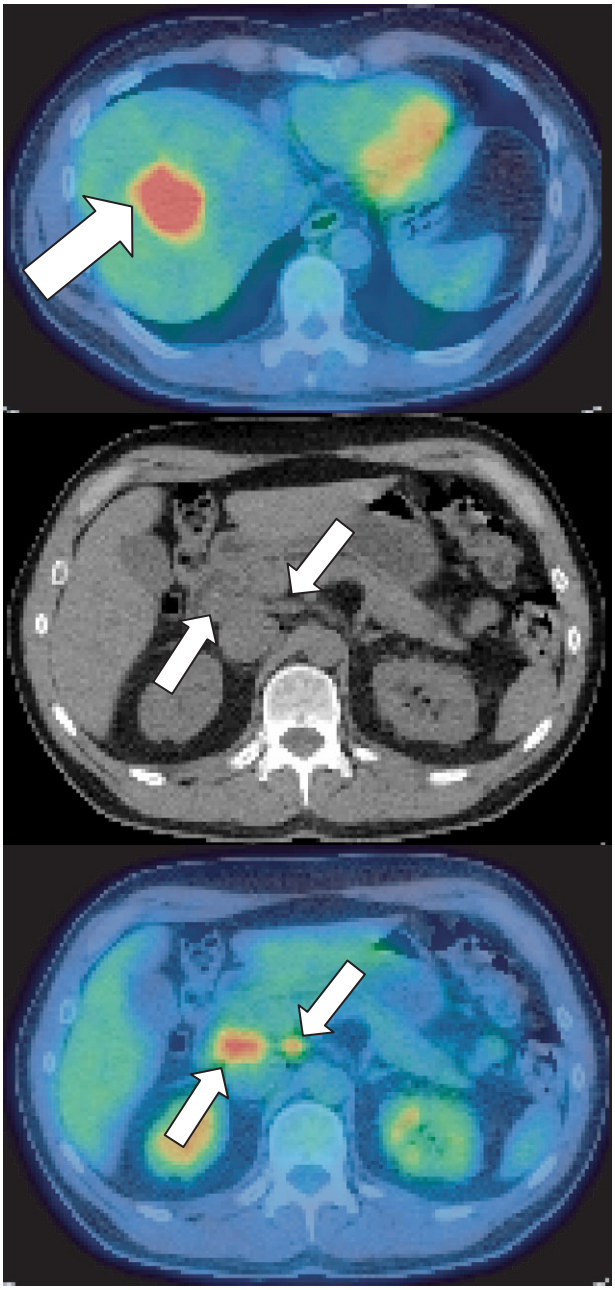

Figure 4 **Diagnostic CT detected a liver metastasis at follow up for colonic carcinoma. PET-CT prior to liver resection confirmed the liver deposit (large arrow) but deemed the patient unsuitable for surgery by demonstrating small lymph node metastases (arrows).**

of 50 colorectal cancer patients found that the technique not only detected a metachronous tumour missed on initial colonoscopy but also identified all patients with local recurrence and distant metastases[20]. However, replicating the promising results of trial centres may not be easily achieved in the clinical environment[21].

Future perspectives: novel imaging biomarkers

Patients entering surveillance programs do not represent a uniform population of equal risk of recurrence. Identification of predictive factors that are linked to outcomes may allow modification of surveillance strategies for sub-groups of patients and the need for research in this area has been highlighted by an expert

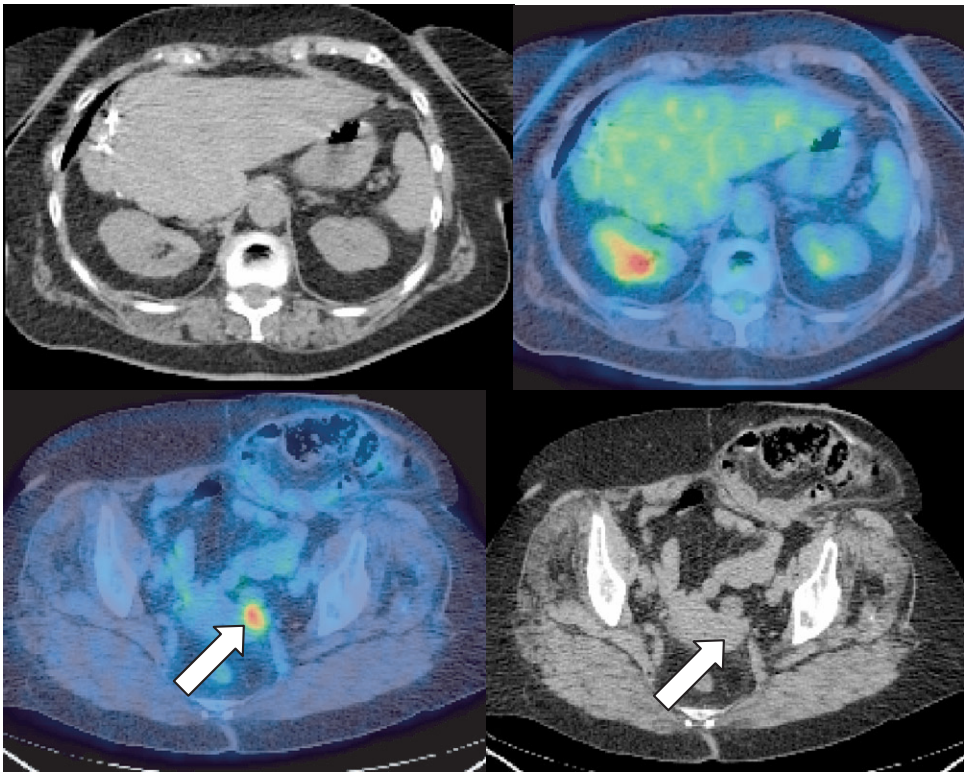

Figure 5 **Colonic carcinoma treated with primary resection and subsequent liver metastasectomy. Two years after the primary resection a rising CEA but normal diagnostic CT led to a PET-CT revealing no evidence of disease at the prior resection sites (see liver images). However an isolated ovarian metastasis (arrow) was detected which was treated by resection and consolidative chemotherapy.**

panel of ASCO[9]. Although several laboratory-derived predictive factors have been identified for patients with colorectal cancer[22,23], biomarkers derived from diagnostic images have received relatively little attention. Recent developments in physiological and molecular imaging techniques have provided new opportunities for the use of imaging as a biomarker[24]. Although not yet widely used in surveillance programs, such techniques do offer considerable promise.

Physiologic imaging techniques that can provide prognostic information for patients with colorectal cancer include assessments of hepatic haemodynamics either with Doppler ultrasound or quantitative analysis of hepatic contrast enhancement on CT[25,26]. The basis for these techniques is the detection of altered hepatic blood flow in association with micrometastases[27,28]. A comparative study has suggested that the different Doppler ultrasound and CT techniques provide similar information[29]. The CT techniques can be readily incorporated into the conventional CT recommended by ASCO whereas the Doppler examination could be added to the ultrasonography advised by ESMO. However, there have been concerns expressed recently as to whether the Doppler examination is generalisable[30].

Quantitative analysis of hepatic CT

A range of techniques have been developed to quantify hepatic enhancement on CT. Simple measurements of liver attenuation or enhancement can be derived using an hepatic region of interest (ROI) drawn from a multi-phase CT study[24]. Alternatively, discrete measurements of hepatic arterial and portal perfusion can be obtained by using a dedicated perfusion CT technique that comprises a series of images acquired without table movement following a bolus of intravenous contrast medium[31,32]. These parameters can also be expressed as the hepatic perfusion index (HPI) which is the ratio of arterial perfusion to combined arterial and portal perfusion. The required processing software is now commercially available.

In a study of 80 patients with a range of primary tumours including colorectal cancer, Platt *et al*. quantified hepatic enhancement during dual- and triple-phase contrast enhanced CT and found that patients who subsequently developed metastases at 18 month follow-up demonstrated increased enhancement both at 25 s and 40 s[26]. The ratio of enhancement at 40 s to peak liver enhancement could identify those patients who subsequently developed overt metastases with an accuracy

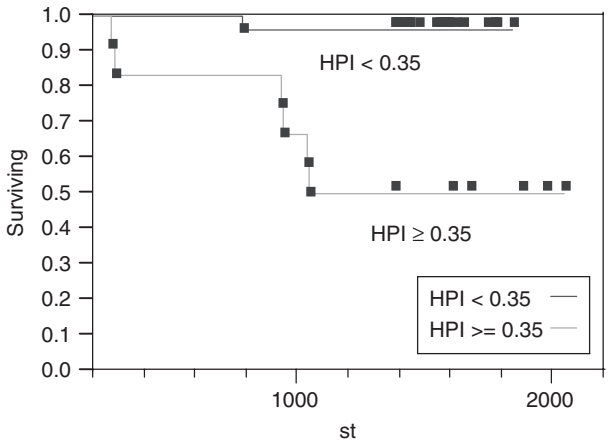

Figure 6 **Kaplan–Meier plots of the survivor function for the hepatic perfusion index (HPI) for patients with no visible metastases on CT[36] (st, survival time in days).**

of 89%. In one study, CT measurements of hepatic perfusion were found to provide an indication of overall prognosis. Following resection of colorectal cancer, patients in whom the hepatic perfusion index (HPI) was greater than or equal to 0.35 demonstrated a risk of death over the subsequent 30 months that was 13.5 times that found when the HPI was less than 0.35 (95% confidence limits 1.6–111, Fig. 6)[33]. The HPI appeared to predict survival more accurately than the original pathological stage as determined from the resected tumour tissue.

Texture analysis of hepatic CT

The human visual system has difficulties in discriminating textural information such as coarseness and regularity that result from local spatial variations in image brightness and a range of computer algorithms have been developed to quantify the textural properties of an image, some of which have been applied to hepatic CT. Apparently normal areas of liver in patients with hepatic metastases exhibit alterations in enhancement and perfusion that are compatible with the existence of microscopic tumour[34]. Texture analysis can demonstrate equivalent changes in patients with metastases but with the benefit of utilising routinely acquired images, thereby avoiding the need for additional scanning[35,36]. Recent work has also demonstrated the potential for texture analysis to provide prognostic information (B. Ganeshan, personal communication).

Summary

The use of imaging for surveillance of colorectal cancer patients is an application of cancer imaging that is supported by evidence-based clinical guidelines. CT provides the mainstay modality for surveillance on grounds of good overall diagnostic performance combined with high availability and low cost, rather than greatest sensitivity for detection of tumour recurrence. Improvements in survival with more aggressive follow up and treatment are likely to demand more accurate imaging techniques in the future.

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