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Colon cancer biology and treatment in the era of precision oncology: A primer for Radiologists☆

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ABSTRACT

In the era of precision oncology, systemic therapies for colon cancer are becoming increasingly biomarker-led, with implications for patients in the neoadjuvant, adjuvant and metastatic settings. As the landscape for colon cancer treatment evolves and becomes more complex, it is important that all members of the multidisciplinary team keep abreast of developments to ensure the most effective care is delivered to patients. As core members of the colorectal multidisciplinary team, Radiologists play a central role throughout the patient journey. This review serves as an educational summary of current and emerging treatment pathways in colon cancer, standards for biomarker testing, mechanisms of action for key drugs, important treatment-related complications, relevant tumour biology that underpins patterns of disease and treatment response, and the specific implications systemic therapies have for cancer imaging and Radiologists. We also highlight the increasing role for radiology in patient stratification and the importance of imaging biomarkers. It is crucial that Radiologists understand the current landscape of colon cancer treatment and emerging strategies on the horizon in clinical trials. Only through engagement across the wider multidisciplinary team will we deliver true personalised medicine for patients with colon cancer.

1. Introduction

Colon cancer (CC) is the commonest abdominal malignancy and a major worldwide cause of cancer-related death. [1] As core members of the multidisciplinary team, Radiologists should understand the key biological characteristics and vulnerabilities of CC that can be exploited by a growing repertoire of treatments, particularly as decision making becomes more complex and personalised. This primer delivers a comprehensive overview of the current roles for radiology, indications and mechanisms of action for current and emerging systemic therapies, the influence of tumour biology on patterns of disease and treatment response, and implications for Radiologists evaluating imaging studies in patients with CC.

2. Colon cancer staging

Computed tomography (CT) plays a major role in the diagnosis of CC and staging of the primary tumour, regional lymph nodes and any

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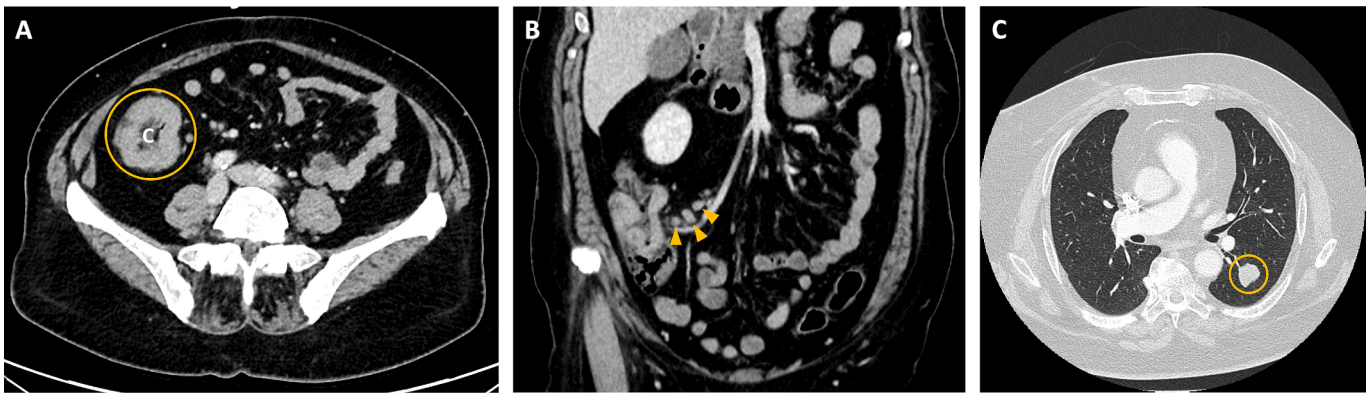

Fig. 1. Radiological Staging of Colon Cancer. Baseline contrast-enhanced CT to confirm clinical TNM staging. A & B) A 61-year-old woman with a locally advanced cancer of the caecum. Axial and coronal images showing wall thickening in an annular tumour with early invasion through the wall (yellow ring) and three enlarged ileocolic lymph nodes (arrowheads) suspicious for metastases. C) A 72-year-old man with metastatic colon cancer. Axial image showing a solitary 2 cm pulmonary metastasis in the apical segment of the left lower lobe (yellow ring). C = caecum.

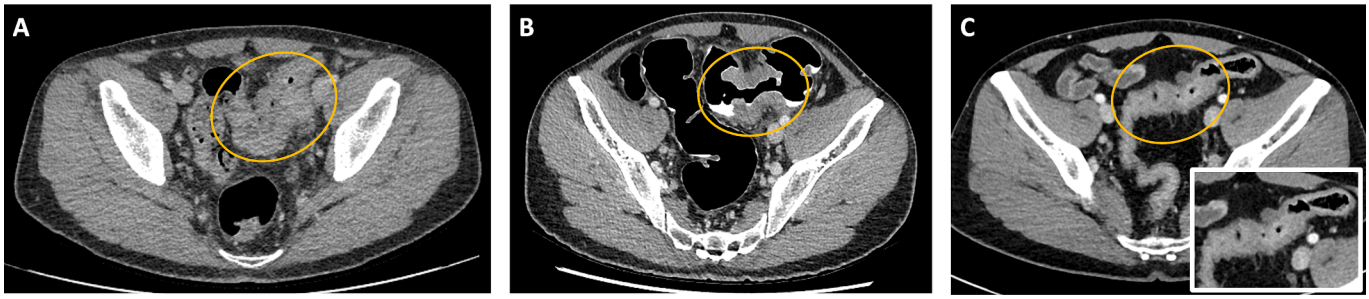

Fig. 2. CT Colonography and Radiological Response to Immunotherapy. A 42-year-old man with mismatch repair deficient colon cancer. Gas insufflation for CT colonography distends the colon and improves delineation of primary tumours. A) Axial image of a sigmoid cancer which is difficult to delineate on standard CT. B) However, CT colonography clearly demarcates the primary tumour. C) Axial image following immunotherapy shows restoration of mucosal and submucosal enhancement with normalisation of bowel wall layers, consistent with mucosal healing and a pathological complete response. Yellow rings placed to indicate the area of the primary tumour.

Table 1
AJCC TNM Version 8 for Colon Cancer.

	Stage		Description
T stage	TX		Cannot be assessed
	T0		No evidence of primary tumour
	Tis		Carcinoma in situ [a]
	T1		Tumour invades submucosa
	T2		Tumour invades muscularis propria
	T3		Tumour penetrates muscularis propria
	T4		Tumour invades non-colonic structures
		T4a	Tumour penetrates visceral peritoneum
		T4b	Tumour directly invades other organs or structures
N stage	NX		Cannot be assessed
	N0		No regional lymph node metastasis or tumour deposit
	N1		Metastases in 1 to 3 regional lymph nodes
		N1a	Metastasis in 1 regional lymph node
		N1b	Metastases in 2 to 3 regional lymph nodes
		N1c	Tumour deposit(s) in the subserosa or non-peritonealised pericolic tissue without any regional lymph node metastases [b]
	N2		Metastases in $\geq$ 4 regional lymph nodes
		N2a	Metastases in 4 to 6 regional lymph nodes
		N2b	Metastases in $\geq$ 7 regional lymph nodes
M stage	M0		No distant metastases
	M1		Metastases in a distant site
		M1a	Metastases confined to one organ (including non-regional lymph nodes) without peritoneal metastases
		M1b	Metastases in more than one organ without peritoneal metastases
		M1c	Metastases in the peritoneum, with or without involvement of other organs

[a] Presence of intramucosal tumour cells without extension to the submucosa.
[b] Tumour deposits are discrete nodules of cancer which lack residual nodal, vascular or neural structures and are found within the adjacent lymphatic drainage area but discontinuous from the primary tumour.[8].

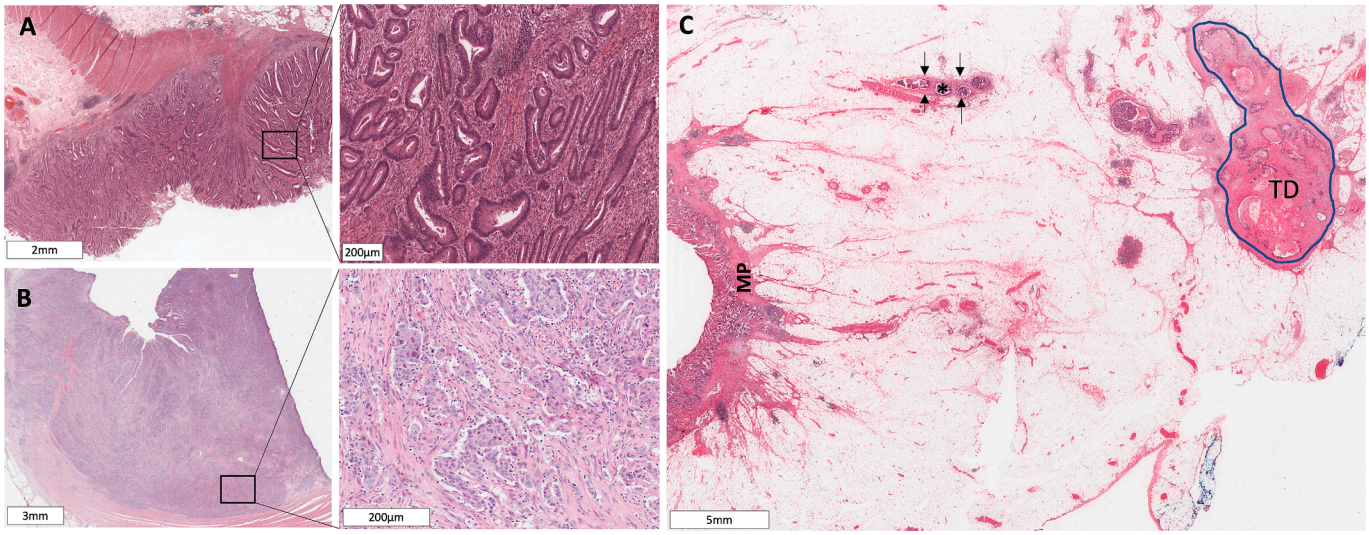

Fig. 3. Pathology assessment of prognostic features. A) Well/moderately differentiated adenocarcinoma of the colon. This tumour is predominantly arranged into glands with lumen which bears resemblance to the architecture of normal colon epithelium. B) Poorly differentiated adenocarcinoma of the colon. In contrast, this tumour is largely composed of sheets of epithelial cells with nuclei showing considerable variation in size and shape with little resemblance to normal colon epithelium. C) EMVI and a subserosal TD associated with a pT3 tumour (2 mm invasion beyond the muscularis propria visible on this image). Tumour cells are seen (black star) within a vein (black arrows) beyond the muscularis propria. The TD (blue outline) is a discrete nodule of tumour discontinuous from the primary tumour with no evidence of lymphatic, venous or perineural invasion. All slides in this figure were prepared with H&E staining. EMVI = extramural venous invasion; H&E = haematoxylin & eosin; MP = muscularis propria; TD = tumour deposit.

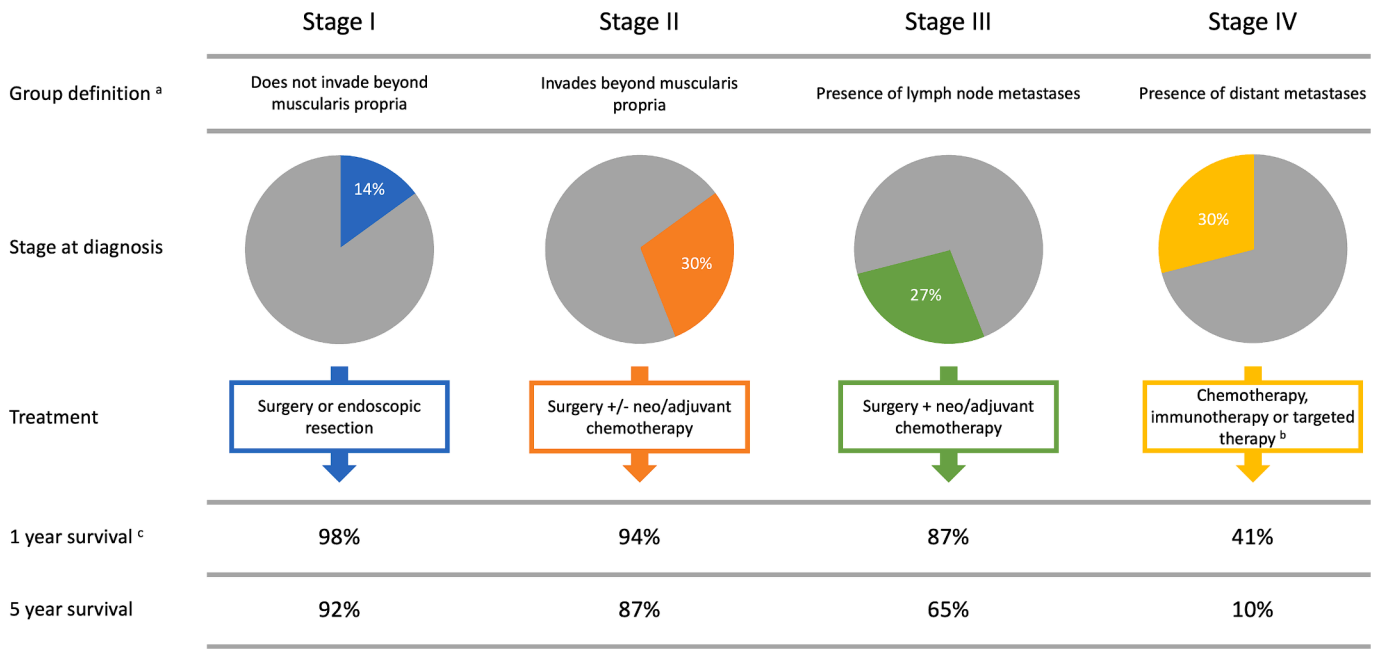

Fig. 4. Colon Cancer Incidence, Treatment and Prognosis According to Staging Group. Colon cancer is staged and grouped using the AJCC TNM system, with implications for treatment and survival.[a] According to AJCC TNM version 8.(6) [b] Some patients with limited metastatic disease may be amenable to surgical resection. [c] Survival data for England from 2016 to 2021.(86).

distant metastases (Fig. 1). While CT of the thorax, abdomen and pelvis is the standard of care for full radiological staging, CT colonography may be utilised as an initial alternative to colonoscopy for tumour detection or to evaluate the proximal colon for synchronous tumours or polyps where stenosis prevents full endoscopic assessment (Fig. 2).[2] Other imaging modalities, including magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT), are typically reserved for abnormalities detected by CT that require further characterisation to confirm or refute metastases.[3,4] While whole body MRI has been proposed as an alternative approach to CC staging, it has not yet been widely adopted in routine clinical practice, primarily due to scanner capacity challenges.[5].

Radiological staging (commonly used as an arbiter of clinical staging) is often denoted by the prefix 'c' (e.g. cT3) and represents a prediction of definitive post-operative pathological staging. Radiological CC staging conforms to the American Joint Committee on Cancer (AJCC) tumour, node, metastasis (TNM) system (current version 8), which is used to guide surgery, any neoadjuvant treatment and prognostication (Table 1).[6] Pathological staging, denoted by the prefix 'p' (e.g. pT3), is derived from the surgical specimen and guides adjuvant treatment

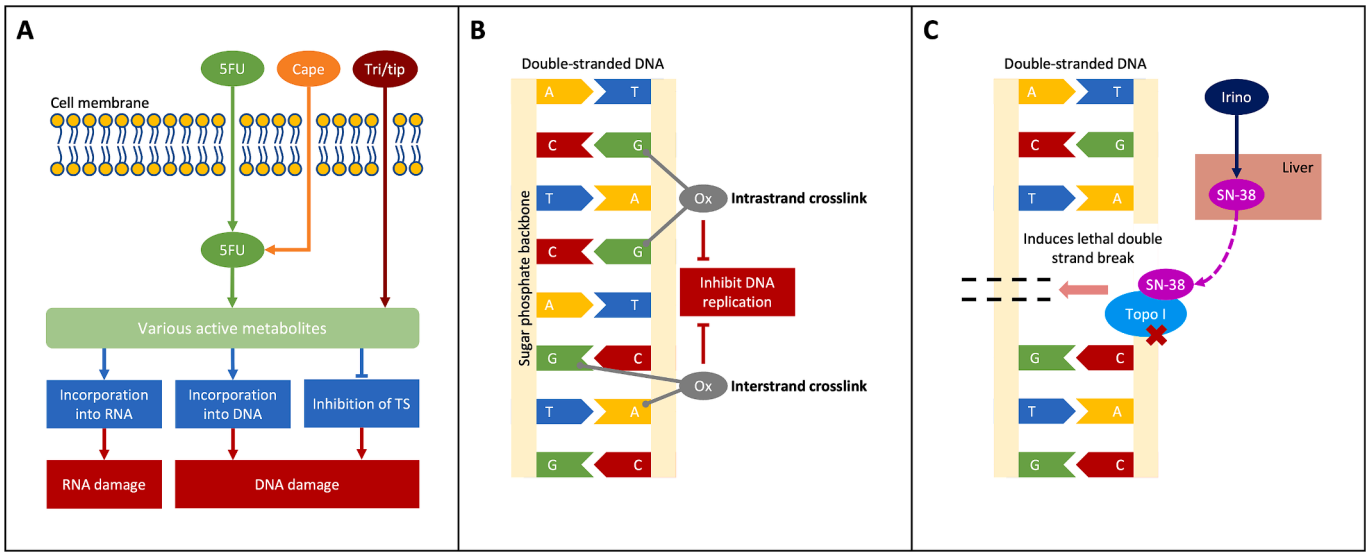

Fig. 5. Chemotherapy Mechanisms of Action. A) 5FU undergoes intracellular conversion to various active metabolites, which induce anti-cancer effects. The prodrug capecitabine is converted to 5FU intracellularly. Trifluridine/tipiracil also undergoes intracellular metabolism before exerting similar effects on cellular DNA and thymidylate synthase. B) Oxaliplatin forms intra and interstrand crosslinks, which inhibit DNA replication. C) Irinotecan is converted to its active metabolite SN-38 in the liver, which binds to topoisomerase I after it has made a single strand break. The resulting complex induces a lethal double strand break and cell death. 5FU = 5-fluorouracil; A = adenine; C = cytosine; Cape = capecitabine; DNA = deoxyribonucleic acid; G = guanine; Irino = irinotecan; Ox = oxaliplatin; RNA = ribonucleic acid; T = thymine; Topo = topoisomerase; Tri/tip = trifluridine/tipiracil. TS = thymidylate synthase.

decisions.[7] Pathological assessment also determines the tumour type, grade of differentiation and the presence of other important features, such as venous, lymphatic or perineural invasion, tumour deposits (TDs) or relevant molecular biomarkers (Fig. 3). If present, TDs are currently only considered as part of TNM lymph node staging, despite evidence of additional adverse prognostic value.[8].

The TNM system also groups CC into four stages. Stage I refers to a primary tumour confined to the muscularis propria without lymph node or distant metastases (T1-2 N0 M0). In stage II CC, the primary tumour extends beyond the muscularis propria but still lacks lymph node or distant metastases (T3-4 N0 M0). Stage III indicates the presence of lymph node, but not distant, metastases (T1-4 N1-2 M0). Finally, stage IV represents CC with distant metastases, irrespective of T or N staging (T1-4 N0-2 M1) (Fig. 4).

3. Principles of treatment

Stage I CC is treated with endoscopic or surgical resection (Fig. 4). Stage II and III (often referred to as locally advanced) CC are treated with surgical resection with or without additional chemotherapy.[7] Adjuvant chemotherapy (AC) is well established for stage II CC with high-risk features (e.g. pT4 staging) and stage III CC, while neoadjuvant chemotherapy (NAC) is now considered a safe and effective treatment option for patients with T3 or T4 tumours on CT.[7,9].

Stage IV (also known as advanced or metastatic) CC is usually incurable and is predominantly treated using systemic anti-cancer therapy (SACT).[10] In select cases, limited metastatic disease may be cured through surgical resection. Primary tumour resection, surgical defunctioning or endoscopic stent insertion may also be used to manage symptoms. Unresectable metastatic CC (mCC) is usually treated with the aim of disease control ('palliative treatment'), which may improve survival, symptoms or quality of life. In this setting, treatments are referred to as 'lines' of therapy (first-line treatment, second-line treatment etc.), where a new line of treatment is given following disease progression. Metastatic colon and rectal cancer are treated similarly with systemic therapies and are therefore often combined as metastatic colorectal cancer.[10].

4. Types of systemic therapy

4.1. Cytotoxic Chemotherapy

4.1.1. Indications and efficacy

Chemotherapy is used differently for CC in the adjuvant, neoadjuvant and metastatic settings.

AC is well established in the treatment of locally advanced CC, where the fluoropyrimidines 5-fluorouracil (5FU) and capecitabine are used, either alone or in combination with oxaliplatin.[7] The benefit of combination adjuvant chemotherapy in stage III CC is clear, where an additional 20 % of patients are cured, compared to surgery alone (approximately 70 % vs. 50 %, respectively).[11] However, the benefit of adjuvant chemotherapy is less evident in stage II CC, a heterogeneous group where individual recurrence risk varies greatly, and over 70 % of patients are cured with surgery alone; current guidance recommends adjuvant chemotherapy only when high-risk features are present (e.g. pT4 staging).[7] Furthermore, with minimal evidence of benefit from additional oxaliplatin in stage II CC, 5FU or capecitabine monotherapy is often used, with combination chemotherapy reserved for those at greatest risk of recurrence.[7,12].

NAC represents a new treatment option for those with T3 or T4 staging on CT. In a recent trial, six weeks of neoadjuvant fluoropyrimidine (5FU or capecitabine) and oxaliplatin, followed by surgery and completion of chemotherapy post-operatively reduced recurrence risk by 28 %, compared to upfront surgery.[9].

The first-line treatment for mCC utilises 5FU or capecitabine alone or in combination with oxaliplatin and/or irinotecan.[10] Subsequent lines of chemotherapy include oxaliplatin or irinotecan-based combinations if not used first-line, irinotecan monotherapy and trifluridine/tipiracil. The efficacy of these regimes varies according to the combination and the addition of any targeted agents. However, the one year survival rate for newly diagnosed mCC is around 40 %.[1] Maintenance chemotherapy and treatment-break strategies may be utilised to limit toxicity and improve quality of life without compromising disease control.[7].

4.1.2. Fluoropyrimidines

5FU is an anti-metabolite chemotherapy delivered as an intravenous

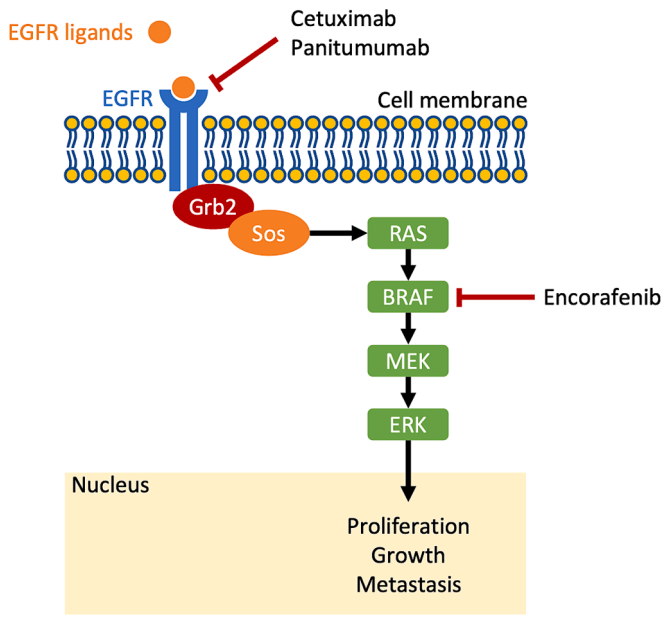

Fig. 6. MAPK/ERK Pathway. Ligand binding of EGFR activates the MAPK/ERK pathway, resulting in cancer-promoting processes. Several agents have been designed to target points in this cellular pathway. EGFR = epidermal growth factor receptor; ERK = extracellular signal-regulated kinase; Grb2 = growth factor receptor-bound protein 2; MAPK = mitogen-activated protein kinase; MEK = mitogen-activated protein kinase kinase; Sos = son of sevenless.

bolus or continuous infusion.[13] 5FU undergoes intra-cellular conversion to several active metabolites, which exert anti-cancer effects by disrupting ribonucleic acid (RNA) and deoxyribose nucleic acid (DNA) synthesis and the function of thymidylate synthase (TS), an enzyme involved in DNA replication and repair (Fig. 5). Capecitabine is an oral prodrug of 5FU taken twice per day and is metabolised to 5FU within tumour cells.[14] Trifluridine/tipiracil is an oral chemotherapy which comprises the fluoropyrimidine trifluridine and tipiracil, an inhibitor of the enzyme which metabolises trifluridine.[15] Like 5FU, trifluridine exerts anti-cancer effects through incorporation into cancer cell DNA and inhibition of TS.

Dihydropyrimidine dehydrogenase (DPD) is an enzyme involved in fluoropyrimidine metabolism and is encoded by the *DPYD* gene.[16] 3–5 % of the general population have pathogenic single-nucleotide

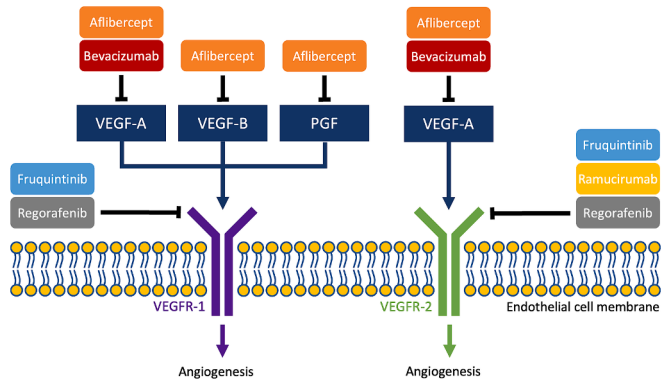

Fig. 7. Inhibition of Angiogenesis. Activated VEGF receptors induce multiple cellular processes, including angiogenesis. Bevacizumab inhibits the action of VEGF-A. Aflibercept inhibits the action of VEGF-A, VEGF-B and placental growth factor. Ramucirumab competitively inhibits VEGFR-2. Regorafenib and fruquintinib inhibit VEGFR-1 and VEGFR-2. PGF = placental growth factor; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

polymorphisms (SNPs) in the *DPYD* gene, leading to DPD deficiency and a risk of significant fluoropyrimidine-associated toxicity. Screening for DPD deficiency is therefore recommended in all patients prior to starting fluoropyrimidine chemotherapy as a dose-reduction or change in treatment may be necessary to prevent complications.[7].

4.1.3. Oxaliplatin

Oxaliplatin is a third generation platinum agent that binds to DNA bases to form crosslinks which inhibit DNA synthesis (Fig. 5).[17] Oxaliplatin has a more favourable toxicity profile than other platinum compounds but peripheral neuropathy affects almost all patients during treatment, and in some cases may become chronic and irreversible.[18].

4.1.4. Irinotecan

Topoisomerases are enzymes that create transient single strand breaks in normal DNA replication.[19] The topoisomerase I inhibitor irinotecan is a prodrug that is converted to its potent metabolite SN-38 in the liver following administration. SN-38 binds to topoisomerase I in tumour cells at the site of a single-strand DNA break, creating a complex which subsequently induces a lethal double-strand break (Fig. 5).

4.2. Targeted Therapies

4.2.1. Molecular Testing as a Standard of Care

Molecular biomarker testing is recommended in all patients with CC. In mCC, testing is performed for mismatch repair (MMR) status and mutations affecting the genes Kirsten rat sarcoma viral oncogene homolog (*KRAS*), neuroblastoma rat sarcoma viral oncogene homolog (*NRAS*) and v-Raf murine sarcoma viral oncogene homolog B (*BRAF*).[10] These biomarkers are primarily used to predict response to targeted therapies but also give insight into prognosis, with *KRAS*, *NRAS* and *BRAF V600E*-muant tumours each associated with poorer survival outcomes.[20] In localised CC, upfront testing is typically limited to MMR status, where MMR deficiency may indicate underlying Lynch syndrome, but is likely to change as targeted agents are investigated in the neoadjuvant setting.[7].

4.2.2. Therapies Targeting the Epidermal Growth Factor Receptor

The epidermal growth factor receptor (EGFR) is a protein found within cell membranes and a member of the human epidermal growth factor receptor (HER) family.[21] Ligand binding of EGFR activates a series of intracellular proteins within the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway to deliver signals to cell DNA, which promote cancer cell proliferation, invasion and metastasis (Fig. 6). EGFR is overexpressed in several cancer types, including CC, and therefore represents an attractive therapeutic target.

The anti-EGFR agents cetuximab and panitumumab bind to, and prevent ligation of, the EGFR receptor and are approved for use alone or alongside chemotherapy in mCC.[10] They are predominantly used in patients with *RAS* wild type (non-mutated), left-sided CC for two reasons. First, mutations in the *RAS* oncogenes (either *KRAS* or *NRAS*) activate the downstream MAPK/ERK pathway irrespective of EGFR ligation, thereby negating the effects of anti-EGFR therapy. Second, only patients with left-sided primary tumours benefit from anti-EGFR therapy, indicating differences in tumour behaviour between left and right-sided CC.[22–24].

4.2.3. Therapies Targeting BRAF

BRAF is a gene that encodes the BRAF protein within the MAPK/ERK pathway. 10–15 % of CCs have *BRAF* mutations, with around 90 % being the *V600E* mutation.[25] Whilst they affect the same MAPK/ERK pathway, *BRAF V600E* and *RAS* mutations are considered mutually exclusive (Fig. 6). However, *BRAF V600E* often coexists with MMR deficiency, a further genetic abnormality associated with CC.[26] *BRAF V600E*-mutant CC represents a particular phenotype, where patients are

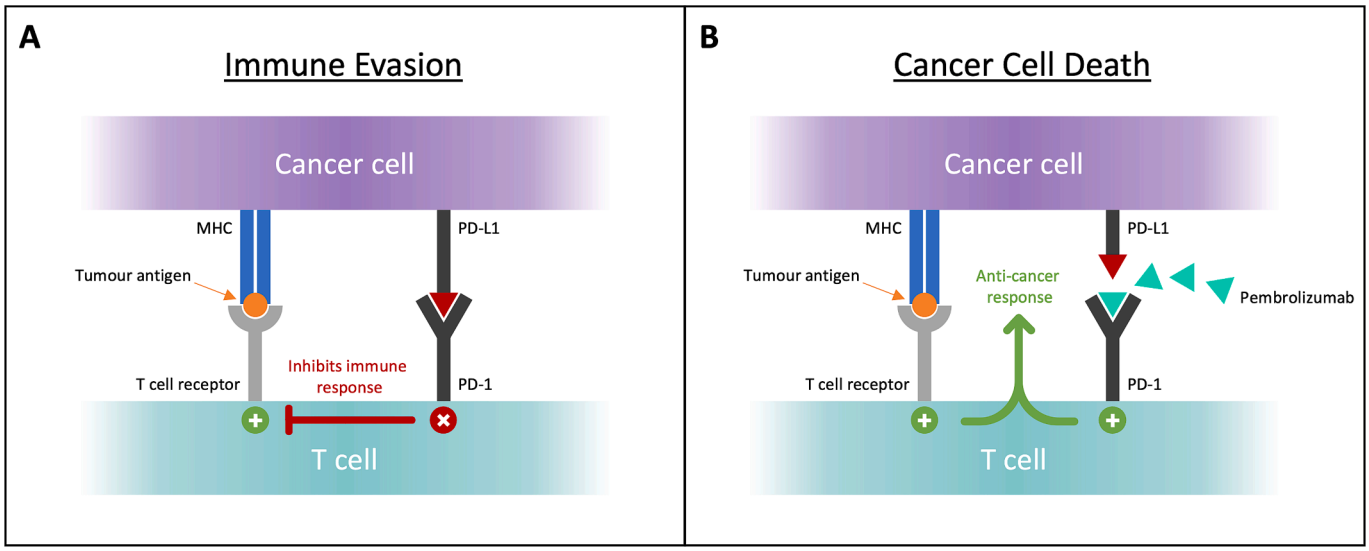

Fig. 8. Immune Checkpoint Blockade. A) Tumour antigens trigger an immune response via T cell receptors. Activation of the immune checkpoint PD-1 by its ligand PD-L1 induces inhibitory signals to suppress the immune response. B) The immune checkpoint inhibitor pembrolizumab competitively inhibits PD-1, allowing the anti-cancer response to proceed. MHC = major histocompatibility complex; PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand 1.

typically older, female and have right-sided, poorly differentiated and mucinous tumours.[25] In the absence of MMR deficiency, these patients also have higher rates of peritoneal metastases and a poorer prognosis, compared to other CCs.[27].

Several anti-BRAF therapies have been developed, with particular success in melanoma.[28] Anti-BRAF therapies provide minimal benefit in CC when used alone, due to feedback activation of EGFR following BRAF inhibition. However, combined BRAF and EGFR inhibition using encorafenib and cetuximab improves overall survival by several months in mCC that has progressed through previous chemotherapy; first-line use of this combination is now being investigated in clinical trials.[29–31].

4.2.4. *Therapies Targeting Angiogenesis*

Angiogenesis is a 'Hallmark of Cancer' and an attractive therapeutic target.[32] New blood vessel formation during angiogenesis is influenced by a variety of factors, including the vascular endothelial growth factor (VEGF) family.[33] VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor are proteins which promote tumour angiogenesis through activation of the tyrosine kinase VEGF-receptors (VEGFR) VEGFR-1, VEGFR-2 and VEGFR-3 (Fig. 7).

Bevacizumab inhibits angiogenesis through inhibitory binding to VEGF-A and improves survival outcomes in mCC when added to first, second, and third-line chemotherapy.[34,35] However, bevacizumab does not improve outcomes when used alongside anti-EGFR therapies.[36] The multikinase inhibitor regorafenib inhibits VEGFR-1 and VEGFR-2 (amongst other proteins) and is associated with modest survival benefits in mCC that has progressed through all other systemic treatments.[37] Emerging anti-VEGF therapies under evaluation include aflibercept, which inhibits VEGF-A, VEGF-B and placental growth factor, ramucirumab, a monoclonal antibody which inhibits VEGFR-2, and fruquintinib, which inhibits VEGFR-1 and VEGFR-2.[38–40].

4.2.5. *Emerging Targets*

HER2 is an established therapeutic target in breast cancer and gastro-oesophageal cancer. Around 5 % of patients with colorectal cancer have HER2-positive tumours, most commonly arising in the sigmoid and rectum.[41] Several early phase trials have tested anti-HER2 agents in treatment-refractory metastatic colorectal cancer, demonstrating promising efficacy. However, while such agents are starting to appear in clinical management algorithms, more definitive data from lager clinical trials are likely to be required for targeting HER2 to become routine practice.[10].

RAS mutations are found in around half of CCs, conferring a poorer prognosis and resistance to anti-EGFR therapies, compared to those which are *RAS* wild type.[20,23,24,27] Several therapies targeting different *RAS* mutations are in active development but the most advanced of these is the *KRAS G12C* inhibitor sotorasib. Recently, the combination of sotorasib with panitumumab was shown to improve progression-free survival in the third-line setting, but overall survival data is awaited.[42].

4.3. *Immunotherapy*

Immunotherapy is an umbrella term used to describe therapies that harness the immune system for anti-cancer effect. Immune checkpoint inhibitors are the most established type of immunotherapy and are used in many cancer types, including CC.[43].

Immune checkpoints are proteins expressed by immune cells which provide either stimulatory or inhibitory signals to fine-tune the immune response when they are activated.[44] This fine-tuning plays a physiological role to regulate the immune response to maintain self-tolerance and prevent autoimmunity. However, cancer cells express inhibitory ligands which suppress the anti-cancer immune response and facilitate 'immune evasion' (Fig. 8). Immune checkpoint inhibitors are monoclonal antibodies which block the activation of inhibitory immune checkpoints to maintain the anti-cancer immune response.

Currently, immune checkpoint inhibitors are only used in MMR deficient (dMMR) mCC.[10] MMR deficiency is associated with several cancer types, including endometrial, ovarian and 10–15 % of CCs.[45] While MMR deficiency is sporadic in 80 % of cases, the remaining 20 % are inherited, in the form of Lynch syndrome. MMR is a mechanism that corrects errors arising in DNA replication. Loss of one or more MMR proteins (MLH1, MSH2, MSH6 and PMS2) disrupts this repair process, leading to an accumulation of mutations. Often, these mutations occur within short sections of repeated DNA known as microsatellites, resulting in the molecular phenotype 'microsatellite instability'.

dMMR CC is associated with right-sided tumours, poor differentiation, mucinous features and an immunogenic tumour microenvironment.[45] Furthermore, dMMR CC is less responsive to cytotoxic chemotherapy but highly sensitive to immunotherapy. The introduction of the immune checkpoint inhibitor pembrolizumab as the established

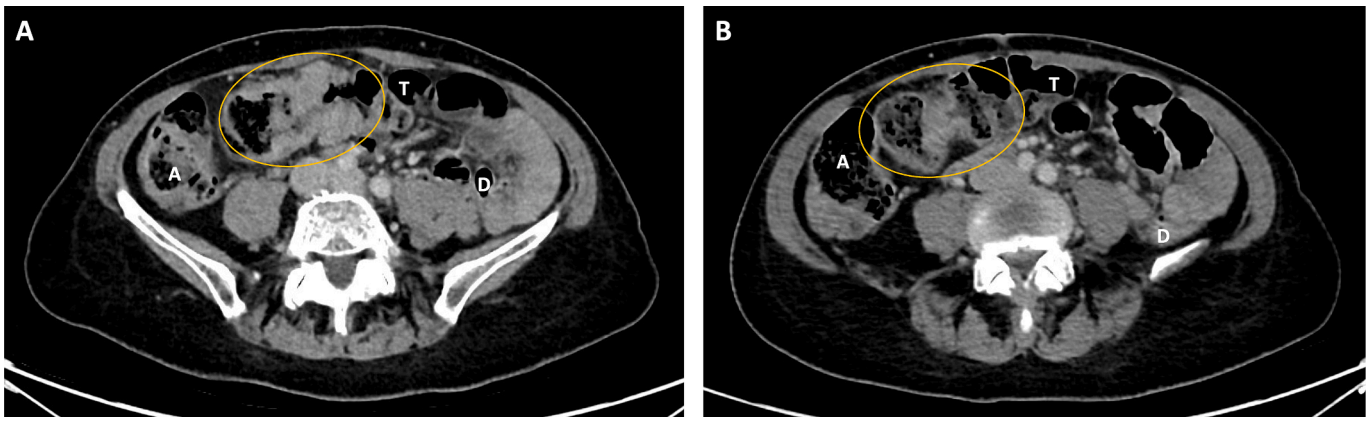

Fig. 9. Radiological Response to Immunotherapy. CT in a 61-year-old woman with a mismatch repair deficient transverse colon cancer. A) Baseline axial image showing a large tumour in the transverse colon. B) Significant reduction in tumour volume following a single cycle of neoadjuvant immunotherapy. Yellow rings indicate the primary tumour. A = ascending colon; D = descending colon; T = transverse colon.

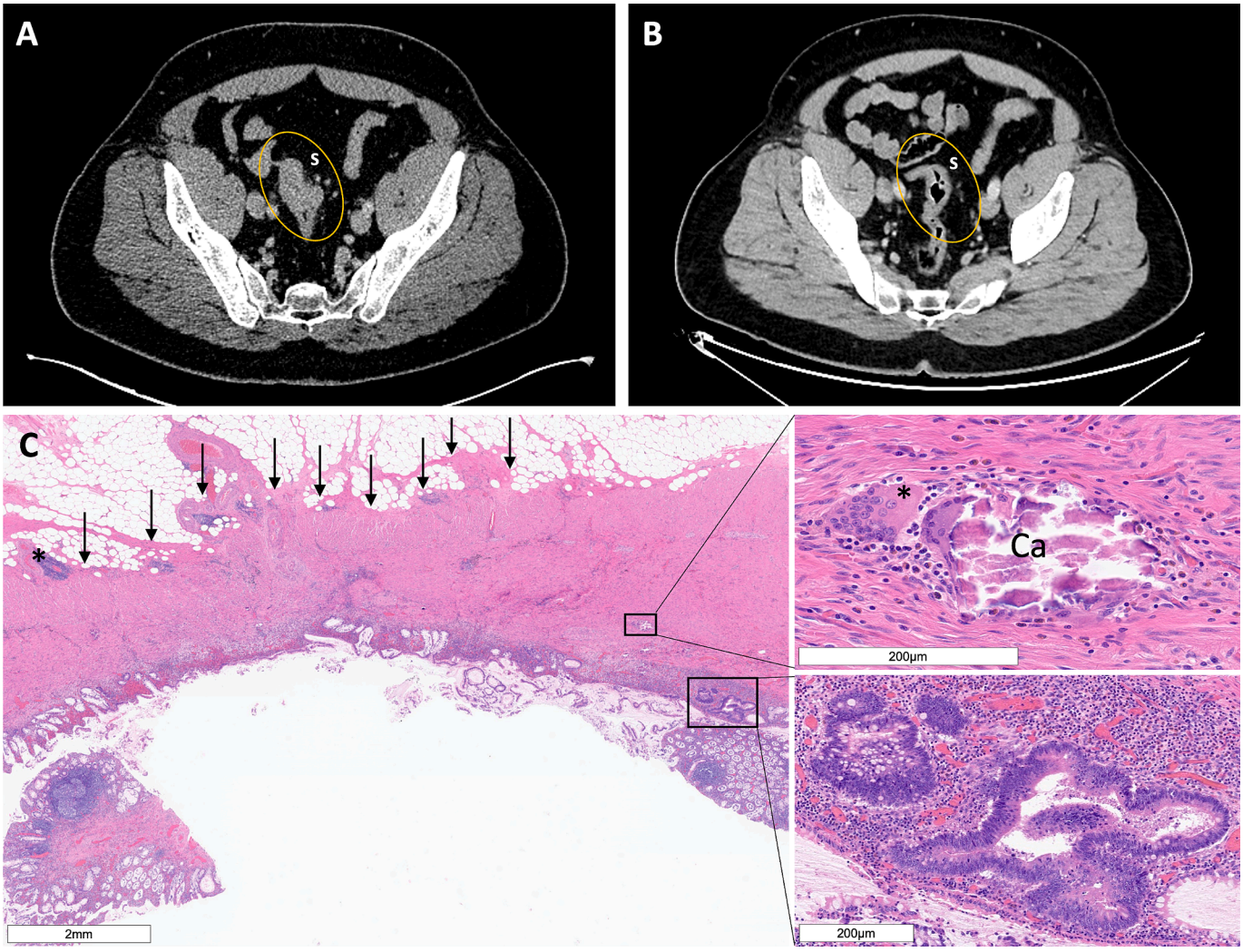

Fig. 10. Radiological and Pathological Complete Responses to Neoadjuvant Chemotherapy. A) Baseline axial image showing a T3 distal sigmoid tumour (yellow ring) in a 45-year-old man. B) Axial image showing a major reduction in tumour volume following 6 weeks of neoadjuvant chemotherapy. C) Overview of pathological complete response with no residual invasive adenocarcinoma. Fibrosis extends into the subserosa (black arrows) and there are multiple aggregates of lymphocytes (example shown with black star) indicating chronic inflammation along with other highlighted features. The top black box shows dystrophic calcification and giant cell reaction (black star) with deposition of calcium (Ca) following neoadjuvant chemotherapy. The bottom black box shows an area of dysplasia of surface epithelium but no evidence of invasion. All histology slides in this figure were prepared with H&E staining. H&E = haematoxylin & eosin; S = sigmoid.

first-line treatment for dMMR mCC has doubled progression-free survival compared to combination chemotherapy.[46] Recently, the combination of two further checkpoint inhibitors ipilimumab and nivolumab was also found to improve survival outcomes, compared to chemotherapy; however, the efficacy of combination, compared to single-agent, immunotherapy is unclear.[47].

The overall risk of recurrence following surgery is lower in localised dMMR CC than MMR proficient (pMMR) CC.[48] Patients with dMMR CC also derive less benefit from adjuvant chemotherapy, which is therefore only used in those at greatest risk of recurrence.[7] NAC does not reduce the risk of recurrence in dMMR CC so is not recommended.[9] Several early phase trials have tested neoadjuvant immunotherapy in localised dMMR CC, with major pathological response rates as high as 95 %.[49] Despite such remarkable efficacy, neoadjuvant immunotherapy is not yet used in routine clinical practice.

5. Implications for imaging in the era of precision oncology

5.1. Staging and Assessment of Primary Tumour Location

The AJCC TNM system is universally recognised but has limitations.[6] Firstly, radiological staging attempts to predict final pathology but achieves limited correlation and accuracy, particularly for lymph node staging.[50] The prognostic value of radiological TNM stage, independent of pathological TNM, is also not well understood. TDs, discrete nodules of cancer within the pericolic tissue, have independent negative prognostic value yet are only recognised within the TNM system in the absence of lymph node metastases (as N1c).[6,51] Finally, the prognostic value of the TNM system is limited by the exclusion of other important features relating to tumour histology (e.g. tumour differentiation), underlying genetics, immune microenvironment and involvement of other local structures.[6].

Endoscopic prediction of the affected colonic segment in CC is limited and CT plays a major role in identifying the true location to help plan surgery.[52] Accurate tumour localisation is also important to differentiate right and left-sided CC, which are distinct entities with differences in tumour biology, aetiology and treatment sensitivity.[53] While the definitions of right and left-sided CC vary, tumours proximal to the splenic flexure are usually considered right-sided and those at, or distal to the splenic flexure, left-sided.[53] Right-sided CCs are associated with MMR deficiency, *BRAF* mutations and resistance to anti-EGFR therapies.[22] Unfortunately, standard CT struggles to identify smaller tumours and those where variable bowel distension and content reduce lesion conspicuity.

5.2. Treatment Response

Treatment response assessment is fundamental to managing mCC. Tumour markers (carcinoembryonic antigen [CEA] and cancer antigen 19–9 [ca19-9]) and symptoms may indicate response but changes in tumour size on CT are primarily used to guide treatment decisions (Fig. 9). Occasionally, other imaging modalities may be used to assess certain sites of disease (e.g. MRI for liver metastases).

The Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria are widely used in clinical trials and provide a standardised framework for describing radiological treatment response. However, there are important limitations relevant to CC; the need for measurable disease at baseline; intra and interobserver variation when assessing CC; the assumption that changes in tumour size equate to treatment response and clinical benefit; lack of recognition for radiological features beyond size (e.g. necrosis or calcification); and not being specifically designed to assess treatment response in luminal tumours.[54] Novel approaches to assessing treatment response include early tumour shrinkage and depth of response.[55] However, whilst these methods appear to be predictive of survival, they lack the prospective data and standardised definitions needed for use in routine clinical practice.

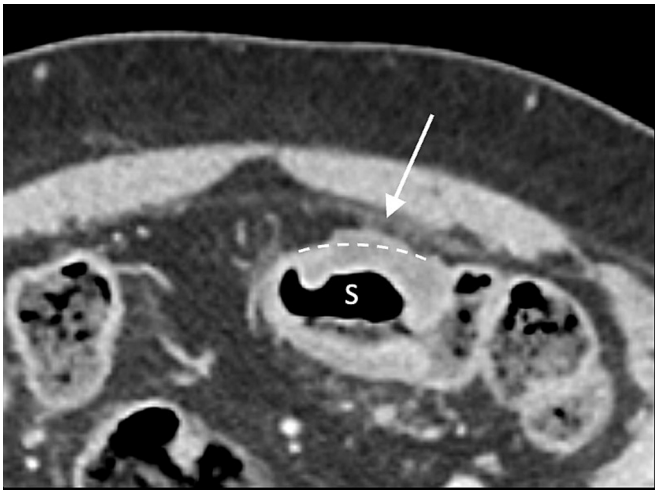

Fig. 11. Sigmoid Cancer with Invasion Beyond the Muscularis Propria. CT scan of a 67-year-old man with a T3 locally advanced sigmoid cancer. The primary sigmoid tumour invades through the full thickness of the bowel wall and into adjacent pericolic fat. The dashed line indicates the position of the outer bowel wall. The arrow highlights the area of invasion beyond the muscularis propria. S = sigmoid.

Assessing treatment response in mCC should therefore consider all available information, including radiological response, tumour markers, change in symptoms and a holistic review of a patient's overall wellbeing.

While most relevant to mCC, the assessment of radiological response has gained new importance in the context of assessing locally advanced CC when using neoadjuvant therapies (Fig. 10).[9] However, there is currently no standardised or validated approach to assessing neoadjuvant treatment response in CC. Any such system would need to be adaptable and applicable to re-evaluating primary tumours with variable and complex morphology.

Pseudo-progression is "radiological progression of lesions that is not confirmed over time, but is followed by a sustained stability or a response to treatment" and is thought to be caused by an accumulation of T cells within a tumour after starting immunotherapy.[56] In mCC treated with immunotherapy, pseudo-progression is estimated to occur in 10 % of patients within the first three months of treatment. The iRECIST criteria were designed to assess response to immunotherapy and mitigate the impact of pseudo-progression, introducing the concept of 'unconfirmed progressive disease'.[57] Differentiating true from pseudo-progression is challenging in clinical practice but Radiologists and Oncologists must be aware of this important phenomenon in CC to avoid the discontinuation of an effective treatment.

Pseudo-residual disease is another novel phenomenon, where apparent residual tumour is seen on imaging despite a pathological complete response to neoadjuvant immunotherapy. The correlation between radiology and pathology in these patients appears limited, presenting a major challenge for non-operative management in those who have achieved a pathological complete response.[58] Translational imaging research from neoadjuvant immunotherapy trials will be critical to improving response assessment in this setting and ensuring safe organ-preserving strategies.

5.3. Imaging Biomarkers

As CC treatment becomes more complex, effective biomarkers must be developed to predict prognosis and treatment benefit. Furthermore, neoadjuvant therapies have placed greater importance on imaging biomarkers to guide pre-operative treatment decisions.[59].

In localised CC, some limited studies have shown radiological T and N stage, tumour deposits and extramural venous invasion (EMVI) to be

Table 2
Treatment Toxicities Relevant to the Radiologist.

Drug	Adverse Effect/Toxicity	Frequency	Potential Role for Imaging	Details
Chemotherapy (5FU, capecitabine, oxaliplatin, irinotecan)	Neutropenia	Common	Investigation of potential complications.	Various imaging modalities may play a role in diagnosing and/or localising infections secondary to neutropenia.
	Diarrhoea +/- enterocolitis	Common	Investigation of potential complications.	CT abdomen and pelvis should be performed to investigate complications of enterocolitis (e.g. perforation). In cases of enterocolitis, CT may show mural thickening, loop dilatation and adjacent fat stranding of the right colon and ileum. Pneumatosis and toxic dilatation are recognised.
	Venous thromboembolism (5FU, capecitabine)	Uncommon	Diagnosis	Depending on the affected vessel, CT or US may be used to identify and diagnose venous thromboembolism.
	Deranged LFTs	Uncommon	Exclusion of alternative diagnoses	US/CT/MRI may be used to investigate alternative causes of abnormal LFTs (e.g. thrombus or unrelated causes like choledocholithiasis).
	Other common/important adverse effects: anaemia, thrombocytopenia, nausea, vomiting, alopecia, fatigue, cardiotoxicity (5FU, capecitabine), PPE (5FU, capecitabine), stomatitis/mucositis (5FU, capecitabine), infusion-related vascular pain (oxaliplatin), peripheral sensory neuropathy (oxaliplatin), cholinergic syndrome (irinotecan).			
Targeted therapies (cetuximab, panitumumab, encorafenib, bevacizumab)	Arterial thromboembolism (bevacizumab)	Uncommon	Diagnosis	Depending on the affected vessel, CT or MRI is used to diagnose arterial thromboembolism/resulting event (e.g. stroke, abdominal organ infarction).
	GI fistula / perforation (bevacizumab)	Uncommon	Diagnosis	CT abdomen and pelvis should be performed for suspected GI perforation/fistula. Findings may include: gas/fluid/contrast within extraluminal collections, air/fluid in the peritoneal cavity, peritonitis, mural thickening, intramural pneumatosis.
	Haemorrhage (tumour-associated or other) (bevacizumab)	Uncommon	Diagnosis	CT or CT angiography may play a role in the diagnosis/localisation of bevacizumab-associated haemorrhage and to plan intervention.
	Other common/important adverse effects: fatigue, diarrhoea, nausea, vomiting, skin toxicity (cetuximab, panitumumab), abdominal pain (cetuximab, panitumumab, encorafenib), arthralgia (encorafenib), hypertension (bevacizumab), impaired wound healing (bevacizumab), proteinuria (bevacizumab), heart failure (bevacizumab).			
Immunotherapy (pembrolizumab)	Diarrhoea +/- colitis	Common	Investigation of potential complications.	CT abdomen and pelvis should be performed to investigate colitis with a suspected complication (e.g. perforation). In cases of immunotherapy-related colitis, mural thickening +/- a fluid filled lumen may be seen on CT. Toxic dilatation is recognised.
	Arthralgia	Common	Exclusion of alternative diagnoses.	XR/US of affected joints may form part of the initial assessment with CT/MRI reserved for treatment-refractory cases. US may demonstrate synovitis +/- joint effusion.
	Deranged LFTs +/- hepatitis	Common	Exclusion of alternative diagnoses.	US/CT/MRI may be used to investigate alternative causes of abnormal LFTs (e.g. thrombus or metastases). In severe hepatitis, CT/MRI may show periportal oedema, altered hepatic attenuation/intensity or perihepatic fluid.
	Thyroid dysfunction	Common	Exclusion of alternative diagnoses.	Nuclear medicine thyroid uptake scan/US may be undertaken to investigate hyperthyroidism. Imaging may show decreased attenuation and/or enlargement of the thyroid gland.
	ILD / pneumonitis	Uncommon	Diagnosis. Exclusion of alternative diagnoses.	High resolution CT chest should be performed in all cases of suspected immunotherapy-related pneumonitis. Several imaging patterns are recognised: organising pneumonia, hypersensitivity pneumonitis, interstitial pneumonia, ARDS.
	Hypophysitis	Uncommon	Exclusion of alternative diagnoses.	MRI head may be performed to exclude other diagnoses (e.g. brain metastases). MRI may show an enlarged and enhancing pituitary gland/stalk.
	Nephritis	Uncommon	Exclusion of alternative diagnoses.	Renal tract US may be used to exclude obstructive aetiology.
	Other common/important adverse effects: Nausea, vomiting, fatigue, rash, pruritis, myalgia, headache, adrenal insufficiency, myocarditis, pancreatitis, diabetes mellitus.			

5FU = 5-fluorouracil; ARDS = acute respiratory distress syndrome; CT = computed tomography; CVA = cerebrovascular accident; GI = gastrointestinal; ILD = interstitial lung disease; LFTs = liver function tests; MRI = magnetic resonance imaging; PPE = palmar-plantar erythrodysaesthesia; US = ultrasound; XR = x-ray.
In the chemotherapy and targeted therapy groups, some toxicities are universal across all drugs. Where most relevant to a specific drug, this is stated in brackets.

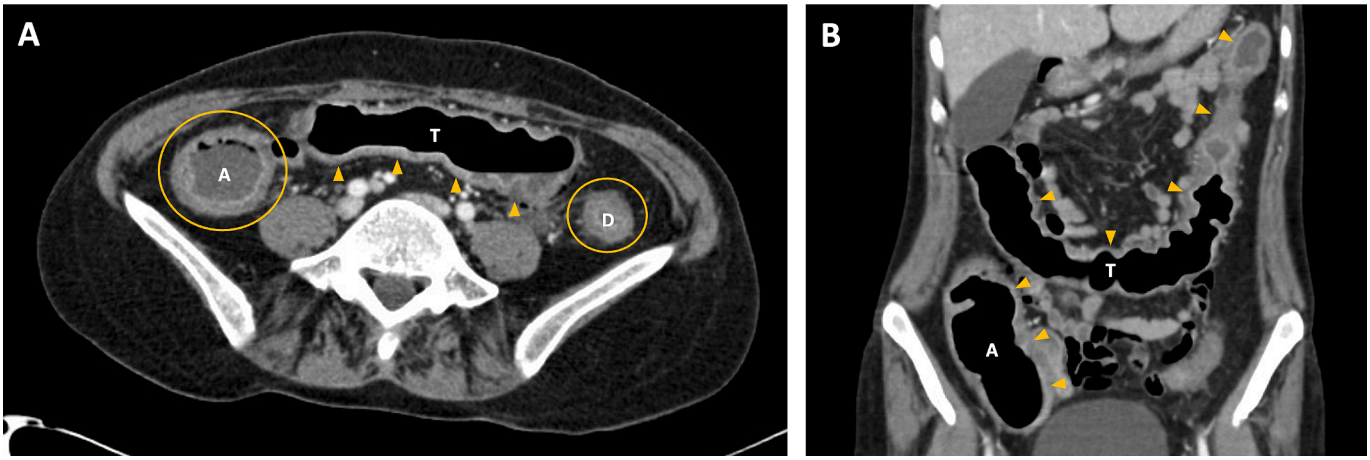

Fig. 12. Immunotherapy-induced Colitis. CT scan of a 61-year-old woman with immunotherapy-induced pancolitis. A) Axial image showing diffuse mural and fold thickening secondary to colitis in the ascending colon, transverse colon and descending colon. B) Coronal image showing mural thickening secondary to colitis in the ascending colon and transverse colon. Yellow rings and arrows placed to highlight areas of colitis. A = ascending colon; D = descending colon; T = transverse colon.

predictors of recurrence risk; yet, these results are not conclusive. [60,61] CT is able to reliably differentiate early from advanced T stage CC (T1/T2 vs. T3/T4), which predicts clinical benefit from NAC (Fig. 11).[9] While some NAC trials have adopted a more detailed approach to case selection, including the degree of T3 tumour extension (e.g. T3 $\geq$ 5 mm), the reliability and value of such precision using CT is currently unclear.[62] Novel approaches, including radiomics and artificial intelligence, are also being researched to provide new insights into radiological phenotyping, but remain experimental.[63].

Imaging biomarkers are not confined to the primary tumour and there is interest in assessing body composition and associated features. [64–66] Whilst these studies are often limited by small, single-centre design and a lack of standardisation, body composition could have important prognostic and predictive value for CC in the future.

5.4. Imaging Phenotypes in Colon Cancer Molecular Subgroups

Evidence is growing around the differences in radiological appearance between CC molecular subgroups. *BRAF*-mutant primary tumours are more likely to have heterogeneous enhancement, shorter length and a polypoid or mass-like morphology, compared to *BRAF* wild type tumours.[67] In dMMR CC, both the primary tumour and regional lymph nodes are larger, and the features most-associated with lymph node metastases different, compared to pMMR CC.[68] Whilst these radiological differences currently have limited clinical relevance, they may be incorporated into novel artificial intelligence algorithms as this field evolves to improve the accuracy of assessment.[69].

Radiomics is a technique which acquires quantifiable information from images beyond what is normally visible.[70,71] Radiogenomics may refer to the use of radiomics to predict the mutational status of tumours. In CC, radiogenomic studies have focused on the prediction of *RAS* and *BRAF* mutations and the presence of MMR deficiency.[72–74] While the current evidence-base is limited to small studies, with issues relating to wider generalisability and clinical relevance, research in radiogenomics is likely to grow.

5.5. Radiological Assessment of Treatment Toxicity and Complications

CC treatments are associated with a range of toxicities which may require radiological investigation. Radiologists should therefore be aware of these toxicities to ensure accurate diagnosis and reporting for the clinical team. Table 2 summarises the common and important toxicities that are most relevant to Radiologists.[12,14,75–83].

Diarrhoea is common with all chemotherapy agents in CC. In severe cases, diarrhoea may indicate enterocolitis related to chemotherapy toxicity or chemotherapy-induced neutropenia.[84] Neutropenia also increases the risk of infection, including those with atypical sites or organisms.

Vascular complications of CC treatment are well recognised. 5FU, capecitabine and oxaliplatin all increase the risk of venous thromboembolism, most often in the form of a pulmonary embolism or deep vein thrombosis.[85] Bevacizumab is associated with rare but important complications, including arterial thromboembolism, haemorrhagic events and gastrointestinal perforation.[78].

Immunotherapy is associated with several recognised immune-mediated toxicities due to physiological immune checkpoint inhibition. Immune-mediated colitis, dermatitis, arthralgia and thyroid dysfunction are relatively common, whereas other toxicities are much rarer, including hepatitis, pneumonitis, myocarditis, hypophysitis and nephritis (Fig. 12).[79].

6. Conclusion

Precision oncology is now established in CC, with increasingly personalised and complex treatment pathways. It is crucial for Radiologists to understand the key aspects of CC biology, and how they are manipulated for therapeutic effect, to best support the wider multidisciplinary management of patients. Whilst there are limitations to current imaging standards, the evolving treatment landscape is likely to drive the discovery of novel imaging biomarkers to enhance care for this patient group.

CRediT authorship contribution statement

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